NNDC 2023 Annual Conference

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NATIONAL NETWORK *of* DEPRESSION CENTERS

NNDC 2023 Annual Conference Poster List

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Outcomes of Transcranial Magnetic Stimulation for Major Depressive Disorder at a Midwestern Academic Medical Center

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Background: 2.8 million adults in the United States had treatment resistant depression (TRD) in 2017. Transcranial magnetic stimulation (TMS) has shown good efficacy and safety in treating patient with treatment of MDD since its Food and Drug Administration (FDA) approval in 2008. Previous "real-world" efficacy data has shown response (>50% decrease in symptoms on self-report scale scores) in 50-60% of patients and remission in 25-30%[1].   Here, we describe our patient population and response to TMS for TRD at a large midwestern academic medical center.

Methods: This was a retrospective study of patients treated with high frequency rTMS to the left dorsolateral prefrontal cortex for major depressive disorder. Each underwent a series of 20-30 treatments, 5 days per week, often followed by a 6-treatment taper over several weeks. Patients with psychotic features or a diagnosis of bipolar disorder were excluded. The Patient Health Questionnaire (PHQ-9) and Beck Depression Inventory (BDI-II) were given prior to the TMS course, and then weekly during treatment. Response (defined as >50% reduction from baseline score) and remission (post-treatment PHQ-9 < 5 and/or BDI-II < 10) rates were calculated. All data are reported as mean(±SD).

Results: Data from 61 patients were analyzed, mean age 55(±14) years, 66% female, 89% white. Mean baseline depression scores were 18(±5) on the PHQ-9 and 35(±11) on the BDI-II, which are in the moderately severe to severe range. Post-treatment scores were 11(±6) on the PHQ-9 and 22(±12) on the BDI-II, respectively. 31 patients (51%) responded and 13 (21%) remitted.

Conclusions: Our response and remission rates are in line with previous retrospective "real-world" analyses for TMS in depression. Further analyses will examine the potential roles of demographics, pre-treatment scores, and treatment history in TMS outcomes, as well as the time course of improvement.

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Outcomes of a Pilot Program on Depression Screening and Post-Screening Intervention in Specialty Clinics at an Academic Health System

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Background: Screening for depression has become more critical in non-mental healthcare settings due to the link between depression and medical comorbidity[1]. However, most screenings are random or only target patients already identified as having a mental health need. Limited mental health resources make it crucial to provide cost-efficient mental health services tailored to patient needs[2]. Our study focuses on two primary objectives. The first is to evaluate the frequency of depression screening through an automated process at specialty clinics within an academic health system. The second is to determine the effects of a two-pronged approach on the type of intervention and follow-up based on the severity score of patients who test positive for depression.

Methods: Eligible patients (aged ≥18 years) who met specific criteria were administered the Patient Health Questionnaire – 2 (PHQ-2) via the patient-facing portal of the Epic Electronic Medical Record, MyChart, over 36 weeks. Those scoring ≥3 on the PHQ-2 automatically reflexed on the Patient Health Questionnaire – 9 (PHQ-9). Patients with PHQ-9 scores ≥10 were considered positive for depression screening. We used a two-prong approach to offer intervention to participants who either had positive depression screen results within 90 days or responded positively to item 9 of the PHQ-9 (thoughts that you would be better off dead or hurting yourself) regardless of their depression score. If patients scored in the range of moderate or moderately severe depression (i.e., PHQ-9 score of 10-19) with a negative response on question #9, they were immediately offered five options for follow-up care through MyChart that included community resources, support groups, or scheduling an appointment with a behavioral health clinician; this was the first prong. If patients scored ≥20 on the PHQ-9 or had any positive response on question #9, they entered an Epic workbench report and were contacted by phone by a behavioral health team member; this was the second prong.

Results: Of the 21,674 patients who were offered PHQ-2 for depression screening during the study timeframe, 38.1% (8,247) completed the screen. We had a positive depression screen in 13.1% (1,084) of the patients screened. In addition, 4.5% (371) of patients screened gave a positive response to item 9 of the PHQ-9. Of the 1,084 patients with a positive depression screen, 44.6% (484) scored in the moderate depression range, 34.4% (373) scored in the moderately severe depression range, and 20.9% (227) scored in the severe depression range. 44.5% (650) of patients were eligible for the first prong of our intervention and were either provided resources or given the option to schedule a behavioral health appointment. 31.1% (455) of patients who completed the PHQ-9 were eligible for the second prong of our intervention (i.e., voice-to-voice phone contact), and 27.9% (127) of patients eligible for the second prong were successfully contacted. This led to 67 scheduled behavioral health appointments, with 45 of these appointments completed. The mean lag time from screening completion to successful contact was 7(±6) days. For those who scheduled an appointment on contact and successfully completed their appointment, the mean lag time from successful contact to appointment completion was 5(±4) days.

Conclusions: Our study shows that implementing automated depression screening through an electronic patient portal yields good depression screening, detection, and follow-up rates. Additional studies are needed to understand the factors surrounding patient willingness to accept mental health resources and interventions and the impact of screening on clinicians.

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[1] Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci. 2011;13(1):7-23. doi:10.31887/DCNS.2011.13.1/wkaton.
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Supercharging Collaboration for Bipolar Research – Breakthrough Discoveries for Thriving with Bipolar Disorder (BD[2])

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Background: Bipolar disorder is a recurrent mood disorder that is estimated to affect up to 4.4% of the global population causing decades of disruption and impairment for individuals and their families. While the disorder is relatively common, clinicians and researchers do not understand the mechanisms that drive the illness which is further complicated by vast differences in how a person experiences bipolar disorder, including heterogeneous profiles of symptom onset, severity, comorbidities, and trajectory. Indeed, we still lack objective, biological measures such as brain scans, genetics, or blood tests that assist in diagnosing the disorder. It is not surprising then that only a subset of patients respond well to current treatments. New methods and comprehensive approaches are needed to identify the modifiable clinical and biological predictors of poor outcome in bipolar disorder.

Methods: BD[2] was publicly launched in September 2022 as a philanthropically-funded scientific initiative housed within the Milken Institute (www.bipolardiscoveries.org). The Integrated Network is one of four programs that comprise BD[2] and represents a novel approach to accelerating discovery science and care for bipolar disorder. It was designed as a Learning Health Network (LHN) with an embedded longitudinal cohort study (LCS). While the LCS facilitates deep phenotyping including clinical and biological measures, the LHN iteratively improves care through cycles of standardized data collection, analyses, and implementation of evidence-based care.

Results: During year one of the program, we identified six US-based clinical sites ideally positioned to form the inaugural cohort. These comprise, Brigham Women's Hospital and McLean; Johns Hopkins University; Mayo Clinical; University Michigan; UCLA; and UT Health Houston. To support standardized data collection across sites and participants, we engaged a Data Coordinating Center (DCC; Indoc Research) and Clinical Coordinating Center (Northwell Heath). Following their recruitment to the program, sites and partners have been involved in a process of co-design and planning prior to participant recruitment, which is expected to commence before the end of 2023.

Conclusions: The Integrated Network of BD[2] brings together research and care in a unique way that sets the stage for personalized care. The ultimate model of change will come from combining these data streams and processes in novel ways. We will facilitate the application of findings from the longitudinal data to care settings intentionally. For example, researchers and clinicians expect that we will identify biologically and behaviorally defined subtypes of people living with bipolar disorder. Based on the profile of the individuals identified, clinicians could partner with researchers to identify and test alternative treatment approaches that are aligned with their biological profile. While these sub-studies are several years away, our infrastructure and network of providers make this vision uniquely possible and rapidly scalable.

National Network of Depression Centers

Decreased Conviction for Self-related Trait-knowledge in Depression

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Background: Distorted self-perception in depression is a well-known phenomenon. Previous work shows that depressed individuals have altered, overly negative thoughts and beliefs about themselves. This abnormal self-evaluation can be difficult to change with treatment and is a risk factor for depression relapse. Separately, depressed individuals show decreased confidence when making decisions compared to healthy controls. It is currently unclear, however, whether adults with depression demonstrate altered confidence when making judgements about themselves and whether they engage in different mental processes when making these evaluations compared to healthy individuals. Understanding alterations in self-evaluation in depression could help to lead to new treatments that could be more effective at preventing relapse.

Methods: Our sample consisted of three groups, a Healthy Control (HC, n=26 fmri, 26 behavioral), a Remitted Depressed (RD, i.e., previously depressed but not currently, n=44 fmri, 43 behavioral), and a Currently Depressed (CD, n=20 fmri, 20 behavioral) group. Participants underwent fMRI scanning while completing behavioral self-evaluation tasks. Specifically, participants rated selected stimuli from the Automatic Thoughts Questionnaire (ATQ), consisting of 20 positive and 20 negative statements (e.g., "I am a failure"). These statements were shown twice: once in reference to the self (e.g., "I have many good qualities") and once in reference to a famous "other," the participant was familiar with but had no relation to (e.g., "Barack Obama has many good qualities"). After seeing this statement, participants were instructed to rate how true they believed the statement to be about the target (Self/Other) on a scale from 1 (Not at All) to 5 (Completely), with a midpoint 3 (Somewhat). Behaviorally, we assessed responses and reaction time (RT). Raw response data were converted into a conviction index. Neurally, whole-brain voxelwise analyses were used to identify clusters of BOLD activation associated with conviction strength as a function of target, group, or their interaction.

Results: Depressed individuals displayed altered conviction-related processing for self-knowledge in three separate ways. First, we observed a group-by-target-by-conviction interaction for reaction times (RT, $F(1,6760) = 5.928$, $p<0.05$); whereas HC responded more quickly with increased conviction for self ratings, the CD group did not; the RD group showed an intermediate pattern between the two. Second, we found a group-by-target interaction ($F(1,6763) = 57.03$, $p<0.0001$) on the degree of conviction participants endorsed, such that in the self condition only, CD and RD groups responded with less conviction than did HC. Third, we observed a group-by-target interaction for BOLD response in a cluster within the visual cortex that tracked with trial-by-trial conviction ratings (k=183, uncorrected $p<0.001$, FDR corrected $p<0.05$, peak voxel: x=-19, y=-91, z=6). In the self-condition HC showed higher levels of BOLD response in this cluster as a function of conviction compared to the CD group, with the RD group intermediate between them.

Conclusions: Adults with depression showed differences in conviction-related processing regarding the beliefs they hold about themselves compared to HC, with RD exhibiting responses intermediate between the two groups. Individuals with depression were slower to respond during self-evaluation even with high-conviction, expressed lower conviction during self-evaluation, and showed decreased neural activation associated with conviction in sensory regions when responding to stimuli about their self-beliefs. These results suggest that depressed individuals may engage in altered processing of self-related information compared to healthy individuals, especially for those self-beliefs that they endorse with higher levels of conviction.

Effect of MRI-guided Low-intensity Transcranial Ultrasound Stimulation on Amygdala Reactivity

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Background: Low-intensity transcranial ultrasound stimulation (TUS) is an emerging non-invasive brain stimulation (NIBS) technique. Compared to other NIBS techniques, TUS allows for deeper penetration and better spatial accuracy. Open challenges include target localization, choice of sonication parameters, and validation of biological effects.
We propose a protocol for a study with the following aims:

- To determine the safety and feasibility of TUS of the amygdala in healthy human participants;
- To design and test an MRI-guided target localization protocol for precise and individualized stimulation;
- To study the effect of TUS of the amygdala on fMRI measures at rest and during an emotional face-matching task.

Methods: 24 healthy individuals will be assigned to two groups with a balanced design (12+12); each group will be assigned to TUS of right and left amygdala, respectively. For each subject, two stimulation sessions will take place one week apart: an active stimulation session and a sham sonication session in a randomized, counterbalanced design. In our preliminary work, we developed an ad-hoc planning software that automatically provides optimal transducer placement immediately prior to treatment through ultrasonic beam simulation based on individual anatomy. For each subject, at the beginning of each session, separate high-resolution (voxel size 1 mm isotropic) structural scans were acquired for amygdala segmentation, ultrasound transducer localization and fiducial localization. Images were then directly fed to an in-house bash-based pipeline that provides image co- registration and generation of left amygdala binary masks through a semantic segmentation neural network architecture. Individualized, MRI-based, predictive transducer placement renderings were generated using custom acoustic modeling procedures (FIELD-II Matlab) designed to be ran iteratively to minimize the distance between the target region and the resulting beam focus. A quick scout MRI scan was performed to confirm the correct placement of the transducer. The targeting procedure has been fine-tuned and validated over 14 scanning sessions.
Sonication will be performed through a single-element ultrasound transducer. An inhibitory sonication protocol will be employed. Resting-state fMRI data will be acquired before, during and after sonication. Task-based fMRI data will be acquired before and after the sonication; the task is a face matching task known to robustly elicit amygdala activation. We hypothesize that TUS will alter amygdala reactivity and amygdala connectivity with other regions involved in affect regulation. We will assess the immediate effect of sonication on anxiety and positive and negative affect. We expect that the inhibitory LIFU-LA paradigm will reduce current state negative affect and anxiety.

Conclusions: TUS is a novel and unique NIBS technique. Our study aims to provide valuable insights that can facilitate the establishment of this intervention in the treatment of psychiatric disorders.

National Network of Depression Centers

Deep brain stimulation for treatment-resistant depression changes plasma metabolic markers

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Background: Approximately 30-35% of depression patients fail to achieve remission despite multiple therapeutic interventions, which is called treatment-refractory depression (TRD). As TRD persists, its burden increases exponentially, with impairments in functional and social functioning, substantial losses in quality of life, and an increased risk of somatic morbidity and suicide. A variety of stimulation-based technologies, including deep brain stimulation (DBS), are emerging as potential therapies for refractory MDD. There is, however, no objective biomarker that can predict clinical response and help with patient selection. Earlier research from our group revealed a link between mitochondrial dysfunction and treatment response in TRD patients, with higher plasma levels of mitochondrial markers. In this study, we evaluate if metabolic/mitochondrial markers (lactate-to-pyruvate ratio, GDF-15, and FGF-21) are biomarkers of treatment response in patients with refractory depression who have undergone medial forebrain bundle (slMFB) DBS.

Methods: Our sample included 12 TRD patients recruited for the Deep Brain Stimulation (DBS) Therapy for Treatment-Resistant Depression - Clinical Trial (NCT02046330). Patients were considered eligible for the study if they met the following inclusion criteria: (a) Major depression, severe, unipolar, diagnosed by SCID-I; (b) Hamilton Depression Rating Scale (HDRS) score > 21 on the first set of items; (c) MADRS score > 21; (d) Global Assessment of Function score of < 45; (e) a recurrent (≥ 4 episodes) or chronic (episode duration ≥ 2 y) course and a minimum of 5 y since the onset of the first depressive episode; (f) age 22–70 y; (g) refractory to > 6 weeks of multiple medication regimens; (h) refractory to > 20 sessions of psychotherapy; (i) refractory to a trial of electroconvulsive therapy (≥ 6 bilateral treatments). Surgical procedure and electrode positions in the superolateral medial forebrain bundle were performed using the Leksell frame (Elekta, Sweden) and following our standard protocol (34, 35). The primary outcome measure was the antidepressant response on the MADRS, where a 50% score reduction was interpreted as a positive response. Plasma samples were collected at baseline and 12 months after surgery. Plasma lactate, pyruvate, GDF-15, and FGF-21 levels were measured using commercial kits.

Statistical analyses were performed using Statistical Package for the Social Sciences, v.23.0 (SPSS Inc., USA). Data distribution normality was assessed using the Shapiro-Wilk test and histogram visualization. Chi-squared was applied to comparisons between the categorical variables. Data with nonparametric distributions were analyzed by the Mann-Whitney U test. The level of statistical significance was set at $p < 0.05$. Due to the exploratory nature of the study, we did not correct for multiple testing.

Results: Our results showed that the mean MADRS score reduction was 58% at 12 months. Seven out of these 12 patients were considered responders (58.3%) with >50% reduction in MADRS scores over time. Our results revealed no changes in the lactate-to-pyruvate ratio (p=0.249), GDF-15 (p=0.811), and FGF-21 (p=0.480) levels over 52 weeks of treatment. On the other hand, we observed that patients who responded to treatment (>50% reduction in MADRS at 1-year follow-up) showed a lower lactate-to-pyruvate ratio than patients who did not respond. Follow-up analyses using paired samples t-tests revealed that in non-responders' patients after 12 months post-surgery, the lactate-to-pyruvate ratio (p=.0085) was significantly lower.

Conclusions: It has been suggested that mitochondrial dysfunction is associated with depression and TRD pathophysiology. We found that non-responders share a common metabolic signature in their plasma before and after treatment. As a metabolic signature, an increased lactate-to-pyruvate ratio could distinguish responders from non-responders preoperatively. In this preliminary study, we cannot exclude type I errors since the sample size is small, and lifestyle factors like physical activity and alcohol use were not controlled. Therefore, our results are exploratory and require replication and validation.

A case of tachyphylaxis following long-term intravenous ketamine for treatment-resistant depression

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Background: Antidepressant tachyphylaxis is a phenomenon described as the loss of response to an antidepressant therapy which was previously effective at an established dose. [1] This can be seen during the earlier phases of the antidepressant administration and during the maintenance phase. The prevalence of tachyphylaxis in Major Depressive Disorder (MDD) remains under-investigated but is estimated to be between 9%-57% in those receiving at least three years of maintenance therapy and affects 25%-50% of those receiving long-term antidepressant therapy.[2,3] We report the first case of tachyphylaxis to intravenous (IV) racemic ketamine for treatment-resistant major depression.

Case Presentation: We present a case of a 56-year-old female with a history of treatment-resistant recurrent MDD, borderline personality disorder (stable), and anorexia nervosa in remission. Her medical history included irritable bowel syndrome, migraines, fibromyalgia, chronic pain, and hyperlipidemia. Her current episode of depression was ongoing for the past 10 years with prominent symptoms of depressed mood, social isolation, low energy, decreased appetite, and anhedonia. No recent suicidal thoughts were reported. Past medication trials included four SSRIs, two SNRIs, bupropion, mirtazapine, two TCAs, phenelzine, mood stabilizers (lithium, valproate, lamotrigine, carbamazepine, topiramate, gabapentin, pregabalin), antipsychotics (haloperidol, aripiprazole, quetiapine, olanzapine), benzodiazepines, eszopiclone, diphenhydramine, trazodone, buspirone, methylphenidate and bitemporal electroconvulsive therapy (16 treatments) with limited benefit. Therefore, we initiated IV racemic ketamine infusions (0.5 mg/kg actual body weight) initially as part of a multisite research study. She completed a three-infusion acute phase trial and a subsequent continuation phase with four weekly infusions. Her baseline MADRS score was 25, decreasing to 2 at the end of the acute and continuation phases. There was a robust and sustained remission of her symptoms for a month. She relapsed after nine weeks and underwent six maintenance infusions within the next 12 months. The duration between the infusions varied from every 4 weeks to up to 12 weeks. In year 3, she received bi-weekly infusions, requiring an additional acute phase of three treatments, for a total of 20 infusions. The treatment interval shortened during year four, and she required 25 infusions. By year five, the patient no longer benefited from ketamine treatment, and despite receiving 15 infusions at biweekly intervals, she remained depressed with a mean QIDS score of around 17-18 (severe depression). Her response to subsequent ketamine infusions diminished and was not sustained for more than a few days.

Results: Sustained clinical response was observed for the first two years of IV ketamine treatment despite ongoing life stressors. In the following years, a gradual reduction of response to subsequent ketamine infusions were observed, with the patient progressively requiring more frequent infusions to obtain the same response. Due to the sustained decrement in ketamine response, the patient and treatment team decided to terminate IV ketamine treatments.

Conclusion: This is the first reported case of tachyphylaxis to IV ketamine for TRD. Tachyphylaxis is a common phenomenon with antidepressants, but so far has not been linked to ketamine treatment. With more widespread ketamine use, it is important to be aware of this potential phenomenon with long-term ketamine use. Ketamine has an addiction potential; thus, it is important to be mindful that increasing the ketamine dosage to address ketamine tachyphylaxis may enhance the potential for undesired consequences.[4,5]

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Update from the NNDC Treatment-Resistant Depression (TRD) Task Group

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Background: Treatment-resistant depression (TRD) is highly prevalent and debilitating disorder, with a strong link to death by suicide. The TRD Task Group, comprised of members from many NNDC member sites, has been working to address important challenges in the field, with the hope of bringing consistent, high-quality treatment to more TRD patients. To date, we have identified three distinct challenge areas. First, our field does not have a consistent, evidence-based standard definition for TRD. A practical framework is sorely needed to bridge epidemiological research, focused studies of TRD, and clinical practice. Second, although specialized academic health center TRD consultation programs can play an important role in improving treatment outcomes by providing access to subspecialists with advanced training and experience in mood disorders, there are many complexities in establishing and sustaining such a clinic. Finally, there is little consensus on what evaluations, assessments, and diagnostic tests should comprise a comprehensive TRD consultation at one of these clinics.

Methods: Utilizing the expertise of our task group members and the support of NNDC via a Momentum grant, we have sought to address by consensus these three challenge areas via smaller multi-disciplinary working groups. Each of these working groups is producing a manuscript for publication to disseminate our work.

Results: Our group has produced drafts of three manuscripts to address the challenges outlined above. The first, "Treatment Resistant Depression: Current Definitions and a Consensus Statement for a New Tracking System," proposes a practical framework called Drugs, Augmentation, Therapy and Advanced Therapies (DATAd), and is currently under revision for publication. Our second manuscript, "Developing a Treatment-Resistant Depression Consultation Program: Consensus Recommendations, Challenges, and Opportunities" addresses systems-level considerations, equity issues, and best practices in the process of taking in referred patients and then returning them to their community providers with a clear plan for ongoing care; it is in final stages of revision prior to submission for publication. Our third manuscript addresses the components of the TRD evaluation itself, including clinical interview, structured and semi-structured assessments, self-report measures, and laboratory and diagnostic workup; it is also in the late stages of revision prior to submission for publication.

Conclusions: It is our hope that through these efforts to build consensus and push the field forward, the TRD task group will contribute to improvement in care for patients with TRD at NNDC sites and beyond. Future task group work will focus on implementation of our consensus recommendations at a group of member sites.

Clinical Features and Polygenic Prediction of Patients with Bipolar Disorder from Latin America

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Background: To date, bipolar disorder (BD) clinic and genetic studies are based primarily on populations of European descent (EUR) and lack representation from other ancestries, including Latin American (LAT). However, accounting for non-EUR populations in psychiatry is vital to address heterogeneity from population diversity and environmental factors. Here, we describe the clinical characteristics and present polygenic-risk scores (PRS) of a new LAT cohort from the Mayo Clinic Bipolar Biobank (MCBB).

Methods: This is a cross-sectional study involving 211 cases and 161 controls of LAT ancestry; and 1,443 cases and 777 controls of EUR ancestry from the LAT cohort of the Mayo Clinic Bipolar Biobank (MCBB), a multisite collaboration with recruitment sites in the United States (EUR site), Mexico and Chile (LAT sites). SCID-confirmed adults with BD1, BD2, Schizoaffective disorder of BD NOS were recruited. Participants accepted and signed informed consent. Clinical data is compared descriptively due to the nature of the study. We applied standard genetic QC and imputed with Michigan Imputation Server using Minimac4 with the TOPMed reference panel. We explored the performance of a BD-PRS in a LAT population. Using results from the most extensive genome-wide association study of BD in EUR individuals, PRSice2 and LDpred2 were used to compute BD-PRSs in the LAT and EUR samples from the MCBB.

Results: For the LAT cohort, the mean (SD) age was 34.7 (13.4) years; they are predominantly women (68.1%), and 69.8% self-identified their race as "Other" and 29.8% as White; 96.4% identified as belonging to a Hispanic ethnic group. Phenotypically, participants were BD I in 56.2% and BD II in 43.8%. 42% of participants reported a history of psychotic mania and 34.2% of suicide attempts. Lifetime psychiatric comorbidity showed predominantly generalized anxiety (38.2%), panic disorder (30.5%), binge eating disorder (22.6%), and posttraumatic stress disorder (14.6%). The most common substance consumption was alcohol (34.5%) and nicotine (33.6%). First-degree relative history was 61.6% for major depressive disorder and 24.7% for BD. Rates of psychosis and other BD traits were similar between EUR and LAT populations, except for suicidal attempts (higher in LAT). Most psychiatric comorbidity was higher in EUR except for anxiety disorders. The LAT sample was younger but had similar rates of overweight and obese patients and higher rates of eating disorders. PRSs explained up to 1.4% (PRSice) and 4% (LDpred2) of the phenotypic variance on the liability scale in the LAT sample compared to 3.8% (PRSice2) and 3.4% (LDpred2) in the EUR samples.

Conclusions: This study shows differences in clinical presentations between BD patients from LAT and EUR ancestry. Although PRS informed with EUR GWAS show better results in EUR vs. LAT participants, different PRS technologies hold the potential to close this gap. International multisite studies, such as this one, have the potential to address diversity-related limitations of prior genomic studies and ultimately contribute to the reduction of health disparities.

Hearing Safety of Accelerated TMS: Calculating Daily Noise Dose of the SAINT Protocol for Depression

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Background: The FDA recently approved the SAINT protocol, an accelerated transcranial magnetic stimulation (TMS) protocol, for depression. 10 intermittent theta burst TMS sessions are administered per day to condense the 90,000 pulse treatment into 5 days[1]. Each TMS pulse generates a brief impulse noise. Pulse sound volume varies with coil design and stimulation intensity, but most reported measurements approach or exceed 85 dB (A), limit A of the US Department of Defense impulse noise standard MIL-STD-1474E[2]. A 6-week course of 3000 TMS pulses per day did not significantly change auditory air conduction thresholds in subjects wearing earplugs[3]. However, the SAINT protocol delivers 18000 pulses per day, a 6-fold increase, and sound exposure standard limits are reported as a function of total daily noise exposure. The hearing safety of increased noise dose in accelerated TMS protocols for patients and TMS operators is not well characterized.

Methods: We calculated the estimated noise dose of the SAINT protocol for the patient and a TMS operator and compared them to safe sound exposure standard limits. Reported peak sound pressure levels for the MagVenture Cool-B65 coil[2] used in the SAINT protocol were scaled per protocol stimulation frequency, intensity, and number of pulses to calculate daily noise dose as a function of distance. For the patient, the distance from a coil placed at the dorsolateral prefrontal cortex (DLPFC) to the ear canal was estimated using reported anthropometric measurements[4] and the EEG-Locator Borckardt/Hanlon System[5].

Results: The loudness for the subject is 93.7 dB (A) calculated at 12.73 cm, the estimated mean distance from the DLPFC to the ear canal. 10 theta-burst sessions are equivalent to 6 minutes total of emitted noise at 50Hz stimulation frequency. The volume for the TMS operator decreases with distance from the coil. At 35cm distance, it falls to 85 dB (A).

Conclusions: The calculated daily noise dose for a patient receiving SAINT is lower than all duration-adjusted occupational noise safety standards identified, including the US Occupational Safety and Health Administration Noise Standard and the EU lower exposure action value[2]. Though it does not meet the strictest threshold in MIL-STD-1474E, limit A, it does meet limit B, the duration-adjusted threshold. If the operator's ear remains at least 35 cm from the coil, their noise exposure meets the most stringent standards for a full 8-hour workday of noise exposure. Standard earplugs rated at 35 dB noise reduction will offer further protection to patients and operators. Of note, this estimate does not account for varying head geometry, bone conduction or time-varying sound damping that may influence true noise level delivered to the ear. Additionally, hidden hearing loss may not be captured with the audiometry studies used to develop occupational exposure limits. Audiologic testing of accelerated TMS patients and operators is needed to establish long term effects on hearing.

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Metabolic and inflammatory biomarkers are linked to the accelerated pace of aging in individuals with bipolar disorder

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Background: Bipolar Disorder (BD) has been previously associated with accelerated epigenetic aging and metabolic dysregulation, although the potential link between these findings is unknown. We hypothesized that accelerated aging in BD is associated with a worse metabolic and inflammatory profile.

Methods: In this study, we assessed a novel epigenetic predictor called DunedinPACE, which predicts the pace of aging. Additionally, we estimated DNA methylation-based surrogates for various metabolic, anthropometric, and inflammatory markers in blood samples. The study included non-psychiatric controls (n=39, 71.2% female) and individuals with Bipolar Disorder (BD) (n=86, 71.4% female) who were matched for age, sex, and race/ethnicity. We computed a metabolic index comprising 14 markers and an inflammatory index consisting of 3 markers, which were positively and negatively associated with metabolic dysfunction and inflammation. To analyze the data, we applied Varimax rotation after performing Kaiser-Meyer-Olkin and Bartlett's tests of sphericity. Furthermore, we divided the patient group into two subgroups based on DunedinPACE scores: high DunedinPACE (n=43) and low DunedinPACE (n=43), for further downstream comparisons.

Results: Individuals with BD showed significantly higher DunedinPACE compared to controls when controlling for age, sex, genetic ancestry, and smoking (p=0.046). Mediation analyses showed significant indirect effects for the composite index of metabolic dysfunction (ab=0.22, BC 95% CI=0.1077 to 0.3616) and inflammation (ab=0.06, 95% CI=0.035 to 0.1013) on the relationship between the diagnosis and DunedinPACE. High pace of aging was associated with significantly higher metabolic dysfunction index in both patients and controls (p<0.001). Specifically in patients, those with high DunedinPACE had significantly higher levels of c-peptide, insulin-like growth factor-binding protein-4, hepatocyte growth factor, adrenomedullin, TIMP metallopeptidase inhibitor 1, plasminogen activator inhibitor-1, growth/differentiation factor (GDF)-15, GDF-8, cystatin C, beta-2-microglobulin, waist-to-hip ratio, body mass index, body fat, interleukin-6, transforming growth factor-α, and C-reactive protein, as well as lower levels of insulin receptor, leptin, HDL cholesterol, and growth hormone receptor compared to those with low DunedinPACE (p<0.001 for all, after Benjamini-Hochberg adjustment for false discovery rate).

Conclusions: Worsening metabolic parameters are associated with accelerated pace of aging in BD, suggesting them as important targets for prevention of aging acceleration and its consequences in patients.

Cognitive aspects of psychomotor abnormalities in depressed adolescents with mood disorders: A systematic review

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Background: Psychomotor disturbances have shown to predict poor treatment response and functional outcomes in adult patients with mood disorders. To highlight the importance of this symptomatology, which reflects both neuromotor and higher-level cognitive components, it has recently been added as the 6th domain to the NIH's Research Domain Criteria (RDoC). Studies in depressed adults have found that motor slowing in depression reflects impairment in initiation, programming, and control of movement and, so, is driven by a cognitive aspect with a distinct underlying neural process involving the dorsolateral prefrontal, anterior cingulate cortex, angular gurus, and basal ganglia. Few studies have examined how these functions are affected in depression during adolescence, an important period of neuronal growth and peak in incidence of mood disorders. The aim of this study was to provide a comprehensive review of studies that utilized objective measurements and neuroimaging to examine cognitive aspects of psychomotor abnormalities in depressed adolescents to identify potential biomarkers that may improve characterization and treatment management in depression.

Methods: Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 GUIDELINES this review was registered in the open science framework (https://doi.org/10.17605/OSF.IO/VJES9). Major databases were searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, from database inception until 01 August 2023 in English language. We included studies of adolescents (range 11-18 years) with depressive symptomatology that examined cognitive aspects of psychomotor retardation in fine motor (eye movements), slower ideation (reaction time of movement), and speech (verbal fluency) domains using objective behavioral tasks and neuroimaging techniques. Conference abstracts, reviews, case studies, conceptual papers, editorials, and book chapters were excluded.

Results: Of 1522 articles, thirty meet the inclusion criteria (n= 4299). The majority of studies were cross-sectional with the exception of 2 longitudinal designs and 1 double bind randomized controlled trial. Six studies included associated EEG data, four studies fMRI data and 2 studies fNIRS. The mean age of depressed adolescents ranged from 11.2 to 17.32 years across studies and from 10.5 to 16.9 years for healthy controls. Four studies examined speech (n= 275), six studies fine motor (n= 529) and twenty-one ideational retardation (n=3564). The most frequent outcome identified was reaction time; however, only one study differentiated initiation time from total time. Findings indicated that depressed participants had slower reaction times which was also associated with disease severity. The consensus of neuroimaging studies revealed significant changes in the fronto-cingulate regions (anterior cingulate cortex, dorsolateral prefrontal cortex) and for EEG data, lower ERN amplitudes (N1) were found in depressed participants and were associated with slower cognitive processing and reaction time.

Conclusions: Our findings align with the adult literature showing impairment of cognitive control of movement in depressed patients during adolescence. Further studies utilizing objective tasks and neuroimaging techniques that differentiate the cognitive and motor component of movement may provide potential biomarkers for improving diagnosis and treatment for adolescents with depression. Considering that adolescence represents a crucial time for cognitive development, cognitive and motor markers could improve the development of tailored treatments to improve functional outcomes in depression. Moreover, studies focusing on the changes in psychomotor functioning across the course of depression throughout the lifespan are needed to determine impacts on functioning.

Brief Cognitive Assessment in Clinical Practice for Youth with Bipolar Disorder

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Background:

Children and adolescents with bipolar disorder often exhibit cognitive deficits that can interfere with social functioning and academic performance and have been shown to have a significant negative effect on long-term outcomes[1]. While substantial heterogeneity in cognition has been found in youth and adults with bipolar disorder[2,3], patients with global and selective cognitive impairments have reported poorer quality of life, more perceived stress, and lower functioning compared to patients without cognitive deficits[4,5]. Therefore, it is important to identify patients with persistent cognitive impairment, characterize the impairment, and implement strategies to address cognitive deficits to improve the clinical management of bipolar disorder. The International Society for Bipolar Disorders (ISBD) Task Force Targeting Cognition recommends that clinicians 1) formally screen cognition in patients whenever possible using brief assessments and 2) evaluate the impact of medication and comorbidity and refer patients for comprehensive neuropsychological evaluation when clinically indicated[6]. Brief cognitive screening is a feasible and efficient method of detecting cognitive impairment in adults but is not routinely used in youth. Few high-quality studies have investigated the utility of cognitive screening in youth[7]. The purpose of this project is to 1) determine the feasibility and utility of incorporating brief assessment of cognition into clinical practice for youth patients with bipolar disorder and 2) collect preliminary data to apply for funding for a larger project to assess and track cognition over time in patients with bipolar disorder to determine which factors are associated with cognitive impairment and the impact on academic and social functioning.

Methods:

Provider Participants: We are recruiting providers that treat patients with bipolar spectrum disorders to complete a survey that assesses provider attitudes toward the assessment and tracking of cognitive symptoms in clinical practice to inform treatment. In addition, the survey assesses provider awareness of assessment tools, understanding of how to use and interpret assessments, and integrating assessments into treatment practice. Providers who refer participants who complete the study will receive a follow up survey assessing a change in attitudes and knowledge.

Patient Participants: We are recruiting youth patients with bipolar spectrum disorders ages 14-25 to determine which factors are associated with cognitive decline and the impact on academic/social functioning. Providers at sites interested in participating can refer patients to participate in the study. Interested participants will be contacted by a research assistant at the University of Utah to schedule a remote visit for 30 minutes. The research assistant will complete informed consent and then administer the Screen for Cognitive Impairment in Psychiatry (SCIP), a brief assessment of cognition, to assess and track cognition. Participants will also complete mood rating scales and questionnaires regarding academic performance and functioning. We will re-assess participants every 3-6 months and provide scores and brief interpretation to providers.

Expected Outcomes:

Strengths of the study design include the use of remote study visits at the Lead Study site to facilitate participation and recruitment at NNDC member sites across the country with minimal burden and to allow for a diverse sample. The expected outcomes of this project will be 1) a manuscript summarizing the results and 2) submission of a NIH grant application and 3) expanding the implementation of brief cognitive assessment for youth with bipolar disorder into clinical care.

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Addressing Racial and Ethnic Disparities associated with Depression Care for Children and Adolescents

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Background: The prevalence of depression in children and adolescents is increasing and has severe impairments that interferes with their development, ability to carry out major life activities and is associated with long-term mental and physical health problems. Depression screening remains controversial among this age group. Currently, the United States Preventive Services Task Force (USPSTF) indicated moderate benefit for screening adolescents aged 12 to 18, but insufficient evidence to screen children 11 years old or younger[1]. Once youth are screened, ensuring adequate and culturally responsive care for children and adolescents with depression remains a challenge. Prevailing barriers for depression care in racial and ethnic minorities include stigma, family beliefs, mental health literacy, and autonomy[2].

Methods: A systematic search of studies using the following databases: APA PsycInfo, EBM Reviews- Cochrane Register of Controlled Trials, EMB-Reviews Cochrane Database of Systematic Reviews, OVID Medline was conducted. Search terms included "depression", "antidepressants", "healthcare disparities", "alternative medicines", and "culturally adapt". Abstracts were manually screened based on the following inclusion criteria: ethnic/racial disparities, depression treatment, cultural interventions and access to care. Abstracts were excluded if there were no measures of depression included, it was not focused on depression care, and the abstract was only focused on depressive symptoms. This systematic search was focused on depression care among children and adolescents, post-partum, late life, and individuals with medical comorbidities from 1990 to June 2023.

Results: From this scoping systematic review, we present the key findings of racial and ethnic disparities that impact depression care for children and adolescents. A total of 1,211 abstracts were screened. A small number of these abstracts focused on racial and ethnic disparities associated with depression care for children and adolescents. Among African Americans, Latinx, and Asian Americans sociocultural factors contribute to differences in depression treatment utilization. A limited number of studies highlighted how different interventions and care models that have been adapted for cultural needs have been helpful.

Conclusions: Our initial review highlights significant racial and ethnic disparities among depression care for several populations, including children and adolescents, despite the progress and novel interventions being used over the past 30 years. We present several recommendations to address disparities in depression care.

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Lamotrigine Co-Administration May Reduce Effectiveness of Intravenous Ketamine in the Treatment of Major Depressive Episodes

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Background: Outcome of intravenous (IV) ketamine treatment may be related to a therapeutic window in its mechanism of action. Thus, coadministration with a drug that may share a similar mechanism of action may alter the effective dose. Both ketamine and lamotrigine (LAM) inhibit the N-methyl-D-aspartate (NMDA)-associated sodium channel in an activity-dependent manner so that co-administration of the two agents may alter the apparent effective dose of ketamine in treatment of depression. There are data suggesting that coadministration of ketamine and LAM may reduce the effectiveness of the ketamine treatment.[1] This was investigated in a new cohort of IV ketamine treated patients.

Methods: We retrospectively evaluated Montgomery Asperg Depression Rating Scale (MADRS) scores in patients receiving IV ketamine with (n = 7) and without (n = 49) co-administration with LAM. The extent of improvement from baseline to 24 hours after the third round of IV ketamine was compared with an unpaired, two-tailed t-test.

Results: Patients receiving LAM (baseline $28.3 \pm$ SD 11.4; after 3rd treatment 18.3 ± 31.4; ns) did not improved to the same extent as patients not receiving LAM (baseline $27.8 \pm$ SD 6.2; after 3rd treatment 10.8 ± 9.0; $P < 0.0001$). The extent of improvement was non-significantly greater in patients not receiving concomitant LAM (total improvement 16.9 ± 9.0 vs. 10.0 ± 1.38, $P = 0.07$, t = 2.01).

Conclusions: While the data are limited by the small sample of LAM-co-treated patients, they support the concept of a therapeutic window for ketamine, and possibly also for LAM. Co-administration of the two medications should be avoided or minimized.

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National Network of Depression Centers

Antidepressant and Stimulant Treatment is not Associated with an Earlier Age of the Incident Case of Mania or Psychosis

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Background: The real-world risk of antidepressants and stimulants changing the trajectory prior to onset of bipolar disorder or schizophrenia is poorly understood. We aimed to analyze the impact of prior antidepressant and stimulant exposure on the age of incident case (AIC) of first episode mania (FEM) or psychosis (FEP) and on duration of illness trajectory (DIT).

Methods: Utilizing the Rochester Epidemiology Project, individuals born after 1985 in Olmsted County, MN, presented with FEM or FEP, subsequently diagnosed with bipolar disorder or schizophrenia were identified. DIT was defined as time from the first mental health visit to FEM or FEP. Duration and peak dose of antidepressant and stimulant exposures were quantified by team consensus. Peak dose of each drug was converted to defined daily dose (DDD), and cumulative exposure was calculated as DDD multiplied by treatment duration. Linear models were used to assess relationships between AIC and DIT with any exposure and cumulative exposure to antidepressants and stimulants.

Results: A total of 190 FEM/FEP patients (27.9% female) were included. Mean AIC was 20.8 ± 3.7 years; this was not significantly different in those with any exposure to antidepressants or stimulants. DIT was longer in patients ever exposed to antidepressants or stimulants (both $p<0.001$). There was a positive correlation between cumulative antidepressant exposure and AIC in whole sample ($r=0.28$; $p<0.001$), and in FEP ($r=0.33$; $p<0.001$) with a trend in FEM patients ($r=0.21$; $p=0.083$). Cumulative stimulant exposure showed no significant association with AIC, also when stratified for the diagnoses. Cumulative antidepressant ($r=0.46$, $p<0.001$) and stimulant exposure ($r=0.36$, $p<0.001$) positively correlated with DIT.

Conclusions: These preliminary findings highlight the need for further investigation into the potential role of antidepressant and stimulant exposure on the trajectory before FEM/FEP.

Posttraumatic Stress Disorder (PTSD) is Associated with Abnormal Amygdala and Striatal Signaling of Temporal Prediction Errors During a Passive Reward Learning Task

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Background: Posttraumatic stress disorder (PTSD) is characterized by prominent symptoms of diminished positive affect (DPA), a transdiagnostic symptom construct largely shared with the diagnosis of major depression. However, unlike depression, the biological bases of PTSD DPA symptoms are not well characterized. Reward processing reliably recruits circuitry implicated in positive affect and is a useful experimental model for the study of DPA symptoms. This includes canonical nodes of the reward circuit, i.e. ventral striatum, ventromedial prefrontal cortex, midbrain nuclei including the ventral segmental area (VTA), as well as limbic structures such as the amygdala and insula. A limited number of prior studies have investigated PTSD reward-processing abnormalities with operant conditioning tasks, which involve choosing behaviors to earn money/points and avoid losses and learning contingencies between behaviors and outcomes. Abnormal neural prediction error (PE) signaling has been observed in PTSD in such tasks, which represents the difference between outcomes expected vs. those received. However, such paradigms only probe PE signaling of reward magnitude/quantity following voluntary choice (operant conditioning). Another critical aspect involves associative learning (classical conditioning), wherein a neutral cue is associated by experience with a rewarding outcome independent of voluntary behavior. Moreover, temporal relationships between predictor and reward can also be learned/acquired and, if violated, leads to temporal PEs (TPEs), which signal the difference between expected vs. actual timing of a reward following a predictive cue. Here, we probed PTSD reward processing abnormalities with functional magnetic resonance imaging (fMRI) to examine brain responses to TPEs during a passive reward learning task in which neutral visual cues were reliably paired with either delayed delivery of a juice bolus (primary reinforcer) or a neutral outcome (another visual cue) 4-6 sec later. A subset were "catch" trials, where the temporal relationship between cue and outcome was extended to 10-12 sec. Through examining distinct temporal windows on catch vs. normal trials, one can map neural signaling of positive TPEs (temporally unexpected outcome received vs. temporally expected outcome received) and negative TPEs (temporally unexpected outcome absence vs. temporally expected outcome absence). We expected PTSD vs. trauma-exposed healthy controls (TEHCs) to display abnormal neural signaling of TPEs.

Methods: Participants with PTSD and TEHC participants (N=45 each) underwent fMRI in a liquid-deprived state and completed two runs of a passive reward learning task. One of two visual cues reliably preceded delivery of a juice bolus (1ml), while the other reliably predicted another neutral visual cue 4-6 sec later. Catch trials were instituted on the second run. Regressors corresponding to onset of each predictive cue, juice bolus, or visual cue outcome were modeled on the first level in AFNI. Contrasts were computed to map positive and negative TPEs for reward (juice) vs. non-reward (visual cue) cue-outcome relationships. Voxel wise independent t-tests comparing PTSD vs. TEHC were constrained by an anatomical mask of the striatum, midbrain nuclei, amygdala, insula, and ventral/subgenual cingulate. T-maps were subjected to probabilistic threshold-free cluster enhancement (pTFCE) at corrected $p < 0.05$.

Results: Relative to TEHCs, PTSD displayed attenuated signaling of positive TPEs (failure to properly activate) in the left amygdala, left midbrain (VTA and parabrachial nucleus), and left ventral putamen. For negative TPEs, PTSD displayed exaggerated signaling (failure to properly deactivate) in the left amygdala and left ventral putamen (all pTFCE $p < 0.05$) relative to TEHCs.

Conclusions: Findings implicate abnormal amygdala and striatal TPE signaling in PTSD, which extends prior findings for abnormal reward PE signaling in operant decision-making reinforcement paradigms. These findings expand knowledge of PTSD circuitry abnormalities and identify potential novel treatment targets for remediating PTSD symptoms of DPA, which are not directly addressed with existing treatments.

An updated meta-analysis of the clinical utility of combinatorial pharmacogenomic testing for adult patients with depression

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Background: Previous studies demonstrate that combinatorial pharmacogenomic (PGx) testing may be a valuable tool to improve clinical outcomes for patients with major depressive disorder (MDD) who have failed at least one treatment. An updated meta-analysis was performed to investigate the clinical utility of combinatorial PGx testing. Prospective studies utilizing a commercially available combinatorial PGx test were meta-analyzed to compare PGx guided care to unguided care in patients with MDD.

Methods: This updated meta-analysis builds upon a previously conducted meta-analysis, which included 1,556 patients from 4 combinatorial PGx studies. Additional studies were identified using PRISMA guidelines. A random-effects model was used to calculate the pooled relative risk ratio (RR) of response and remission.

Results: Overall, 3,532 patients were included from six studies, with outcomes evaluated at week 8 or week 10. Patient outcomes were significantly improved for patients with MDD whose care was guided by the combinatorial PGx test results compared to unguided care (response RR = 1.30, 95% CI: 1.16–1.47, $p < 0.001$; remission RR = 1.41, 95% CI: 1.19–1.66, $p < 0.001$).

Conclusions: Access to a combinatorial PGx test improved response and remission rates among adult patients with MDD who experienced at least one prior treatment failure. These findings further demonstrate the clinical utility of combinatorial PGx testing for the treatment of MDD and suggest that health care providers may observe significantly increased response and remission rates when using combinatorial PGx testing to inform medication selection in patients with MDD and one treatment failure.

Familiarity with psychiatric pharmacogenomic testing in physicians and advanced practice providers: educational opportunities

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Background: Pharmacogenomic (PGx) testing identifies individual genetic variation that may inform medication treatment. Lack of awareness and education may be barriers to implementing routine PGx testing. To characterize current PGx testing utilization and educational needs we conducted a survey of various provider types.

Methods: Healthcare providers in the primary care setting were targeted between November 2022 and February 2023 via the Medscape Members paid market research program. The survey included 5 demographic, 5 multiple-choice, and 4 multi-component five-point Likert scale questions to assess PGx sentiments, use, and education in mental health (e.g., depression) and primary care (e.g., cardiovascular disease) conditions. Responses were descriptively compared.

Results: Of 305 U.S. provider respondents [40% nurse practitioners (NPs), 33% frontline MDs/DOs, 3% physician assistants (PAs), 24% other], most indicated that they "don't use" (44-49%) or "have never heard of" (19-20%) PGx testing for mental health conditions. The most helpful sources to learn about PGx testing were accredited CE/CME activities (55-61%) and peer-reviewed publications (57-59%). Most NPs/PAs preferred webinars (62%) or online learning portal (57%) formats. MDs/DOs had no preference for webinars or learning portals over conferences, written materials, or academic presentations (45-47%). NPs/PAs were more interested in learning about PGx testing than MDs/DOs (4.29/5 vs. 3.96/5 average score).

Conclusions: These data reveal awareness level and desired learning opportunities for PGx testing between types of healthcare providers. Education should be tailored to meet providers' preferred learning formats and information sources, such as offering CE/CME through an online learning portal.

Utilization of psychiatric pharmacogenomic testing by primary care physicians and advanced practice providers: confidence and implementation barriers

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Background: Pharmacogenomic (PGx) testing identifies individual genetic variation that may inform medication treatment. Sentiment and barriers may limit PGx testing. Here we compare confidence in utilizing PGx testing and barriers to implementation by type of provider and treatment condition as identified in a survey.

Methods: Healthcare providers in the primary care setting were targeted between November 2022 and February 2023 via the Medscape Members paid market research program. The survey included 5 demographic, 5 multiple-choice, and 4 multi-component five-point Likert scale questions to assess PGx sentiments, use, and education in mental health (e.g., depression) and primary care (e.g., cardiovascular disease) conditions. Responses were descriptively compared.

Results: Of 305 U.S. provider respondents [40% nurse practitioners (NPs), 33% frontline MDs/DOs, 3% physician assistants (PAs), 24% other], 32% of NPs/PAs and 29% of MDs/DOs had used PGx testing for mental health conditions. The major barriers to adopt PGx testing were similar for mental health and primary care conditions yet differed by provider type. NPs/PAs (72-77%) were more concerned with patient cost than MDs/DOs (46-55%), whereas MDs/DOs were more concerned with evidence of clinical utility (54-59%) than NPs/PAs (40-42%). In respondents who use PGx testing, MDs/DOs reported slightly more confidence utilizing PGx than NPs/PAs. For both groups, confidence in using PGx for mental health conditions was somewhat greater than for non-mental health conditions.

Conclusions: These data illuminate the implementation barriers and confidence levels of clinicians utilizing PGx testing. Increasing awareness around patient cost and evidence of clinical utility for PGx testing may improve utilization.

How does psychedelic use impact mental health in patients with bipolar disorder?

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Background: Amidst the resurgence of psychedelic research, individuals with bipolar disorder (BD) have been notably absent from clinical trials due to concerns about treatment emergent adverse events such as manic switches or psychosis. This observational study employs a calendar-based approach to examine the effects of recreational psychedelic use on mental health symptoms and substance use in patients with BD. By addressing concerns of heightened safety risks, this investigation seeks to contribute to the ongoing reevaluation of including patients living with BD in the growing field of psychedelic research.

Methods: So far, 99 participants who have used a classic psychedelic have been deemed eligible for analyses after completion of a Timeline Follow-Back (TLFB) interview. During this interview, participants retrospectively reported the days with mental health symptoms and substance use, spanning one month before (baseline month) and three months after using the psychedelic. All were 18 years or older with a confirmed diagnosis of BD. Participants were excluded from analysis if they could not remember the 4-month period asked of them via the TLFB.

Results: In these users, we found significant differences (using Friedman χ^2 ANOVA) between baseline (i.e., 1 month before psychedelic use) and the 3 months post psychedelic use for number of days with 1) no mental health symptoms, 2) depressive symptoms, and 3) alcohol use. There was no significant increase or decrease observed for number of days with mania, psychotic symptoms, anxiety, prescribed medication use, or psychiatric hospitalizations.

Conclusions: Our findings have thus far not revealed any substantial adverse outcomes of psychedelic use among patients with BD. Rather, our analyses indicate an improvement in their mental health symptoms in the months following a psychedelic experience. When considered alongside preliminary results from Aaronson et al.'s pilot study of psilocybin's effects on BD-II depression, our results suggest it may be feasible and safe to further investigate the therapeutic potential of psychedelics in patients, at least those with BD-II, within a controlled environment.

Longitudinal Blood Transcriptomic Changes In Hospitalized Mood Disorders Patients With Suicidal Ideation

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Background: Suicide is a complex multifactorial event resulting from an interaction between biological and psychosocial factors. Identifying the molecular basis of suicidal ideation (SI) may provide targets for the development of novel treatment strategies and help better identify patients at risk of suicide.

Hypothesis/Goals: We aimed to longitudinally characterize the transcriptomic dynamics of peripheral blood mononuclear cells (PBMCs) in hospitalized patients with mood disorders admitted due to acute SI. We hypothesize that improvement of SI is associated with significant changes in blood gene expression and blood cell composition.

Methods: We recruited forty-two patients with mood disorders, ages 18 or older, hospitalized with SI as a significant aspect of their presentations (Beck Scale for Suicidal Ideation (BSS) > 4). All subjects provided blood samples upon admission (T1) and immediately before discharge (T2). Bulk and single-cell RNA sequencing was performed at the two time points in N=15 and N=3 patients with significant improvement of SI (> 50% of reduction in BSS scores between T1 and T2), respectively, using Illumina 2x150bp sequencing and 10X Genomics Chromium[TM] 3' gene expression system. Paired analysis compared gene expression between T1 and T2 with correction for multiple comparisons. The levels of different blood cell types were estimated with transcriptomic data by cell-type deconvolution analysis.

Results: Twenty-six patients showed significant improvement of SI during hospitalization (mean (SD) BSS scores were 17.8 (8.31) at T1 and 1.0 (4.75) at T2). 'Non-improvers' had a mean (SD) BSS score of 21.3 (6.36) at T1 and 16 (7.75) at T2. No demographic or clinical variables at baseline were different between the two groups of patients. Three genes were differentially expressed between T1 and T2 (FDR=0.10) in patients that showed SI improvement, including *ZNF704* (logFC=1.70), *STMN1* (logFC=0.49), and *DDIT4* (logFC=0.67). Changes in BSS significantly correlated with changes in ZNF704 expression (r=0.597, p=0.019). The levels of B-cells and monocytes were significantly down-regulated at T2 compared to T1, while the levels of natural killer (NK) and T-cells were up-regulated (p < 0.05 for all). Specifically, the levels of the classical CD14+ monocytes were downregulated while the levels of the non-classical CD16+ monocytes were downregulated (p < 0.05) alongside SI improvement.

Conclusions: SI symptom improvement could not be predicted by demographic and clinical variables at baseline, but was associated with significant blood transcriptomic changes. Symptom improvement was associated with major blood cell changes and specific changes in monocyte subtypes.

Electroconvulsive Therapy at a Crossroads: Risk Stratification in a Challenging Case of Depression versus Pseudodementia

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Background: It is unclear if medication-resistant late-life depression is distinct from major depressive disorder, or a theoretical variant. The pattern of late-life depression is often complicated by cognitive impairment, which could be reflective of a pseudodementia or a superimposed neurological disorder. Whether the depressive diagnosis is distinct, co-morbid with cognitive decline, or causal of a dementia-like state, we aim to demonstrate that electroconvulsive therapy (ECT) remains a highly efficacious treatment.

Methods: We present the complexities of an ECT "decision for case" and complications during ECT for a 82-year-old male admitted for depression with progressing mood symptoms that worsened significantly over the years and were resistant to medications. Symptoms resulted in self-neglect and a fluctuating neurovegetative and neurocognitive state. His symptoms of depression and comorbid behavioral disturbance evolved over time, as his psychomotor progressed to potentially early signs of catatonia, posing another diagnostic dilemma. A prior history of dementia was not documented. Although there was a remote history of possible stroke, CT of head did not identify an organic correlate. His case was further complicated by an extensive cardiac history, including coronary artery disease, atrial fibrillation on apixaban, and hypertension. As his medical conditions made him a high-risk ECT candidate, a clear, well-explored risk stratification was critical.

Results: Improvements in patient's interests, motivation, and self-care were noted after he received an index series of ECT. However, ECT was interrupted for two months due to issues with insurance coverage and his symptoms notably worsened, particularly anhedonia and psychomotor retardation, as a result. The patient underwent a series of ECT and experienced expected, but concerning, physiological cardiac effects arising from the combination of sympathetic and parasympathetic outflow during his ECT procedures.

Conclusions: This case highlights the importance of maintaining a broad differential as it pertains to risk stratification in ECT and treating a patient with a history of cardiac dysfunction. The patient's behavioral disturbances worsened with the temporary cessation of ECT and improved with its continuation, hinting at elements of pseudodementia, as in MDD or late-life depression. Given the severity of his initial symptoms and response to ECT, it was important to pursue treatment with continuous monitoring of his cardiac dysfunction by maintaining collaborative efforts among psychiatrists and primary care teams. For future directions, it would be beneficial to monitor the progression of his cognitive impairment with MOCA or SLUMS exams as he receives additional ECT sessions.

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Epigenetic GrimAge acceleration and cognitive impairment in bipolar disorder

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Background: Bipolar disorder (BD) has been previously associated with clinical signs of premature aging, including accelerated epigenetic aging in blood and brain, and a steeper age-related decline in cognitive function. However, the clinical drivers and cognitive correlates of epigenetic aging in BD are still unknown. We aimed to investigate the relationship between multiple measures of epigenetic aging acceleration with clinical, functioning, and cognitive outcomes in individuals with BD and controls.

Methods: Blood genome-wide DNA methylation levels were measured in BD individuals (n = 153) and matched healthy controls (n = 50) with the Infinium MethylationEPIC BeadChip (Illumina). Epigenetic age estimates were calculated using an online tool, including the recently developed lifespan predictor GrimAge, and analyzed with generalized linear models controlling for demographic variables and blood cell proportions.

Results: BD was significantly associated with higher GrimAge acceleration (AgeAccelGrim, β=0.197, p = 0.009), and significant group-dependent interactions were found between AgeAccelGrim and blood cell proportions (CD4+ T-lymphocytes, monocytes, granulocytes, and B-cells). Within BD individuals, higher AgeAccelGrim was associated with worse cognitive function in multiple domains (short-term affective memory (β=-0.078, p = 0.030), short-term non-affective memory (β=-0.088, p = 0.018), inhibition (β=0.064, p = 0.046), and problem-solving (β=-0.067, p = 0.034)), age of first diagnosis with any mood disorder (β=-0.076, p = 0.039) or BD (β=-0.102, p = 0.016), as well as with current non-smoking status (β=-0.392, p < 0.001).

Conclusion: Our research has shown that BD is significantly associated with higher AgeAccelGrim than controls, but not with other epigenetic markers investigated. Furthermore, we found that a higher AgeAccelGrim was significantly linked to cognitive dysfunction and current smoking status among individuals with BD. Overall, our findings support the contribution of epigenetic factors to the aging-related cognitive decline and premature mortality reported in BD individuals, with an important driving effect of smoking in this population.

Electroconvulsive Therapy in Patients Without IV Access: Usage of Totally Implantable Vascular Access Devices
Abstract

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Background: We present the case of a 42-year-old female who is actively receiving electroconvulsive therapy (ECT) for treatment refractory depression. Two prior ECT series resulted in excellent responses with negligible side effects. During this current series of ECT, there was significant difficulty in obtaining venous access each session with multiple failed attempts by nursing staff and anesthesia, including technological aids (i.e., ultrasound) leading to patient discomfort and greater procedural resource utilization.

Methods: After deliberation with the patient and treatment team, the decision for placement of an alternative vascular access device (VAD) was made. A totally implantable vascular access device (TIVAD) was chosen given the expected frequency and number of treatments, lower maintenance compared to other VAD, and previous success in patients undergoing ECT.[1-4] Due to a communication error at the level of primary care to interventional radiology, a central venous catheter (CVC) was placed instead of a TIVAD. ECT began with anesthetic agents administered via the CVC, but gradually after a series of treatments, the patient reported difficulty with the upkeep, pain and erythema at the CVC site, and dressings were noted as unclean (placing her at higher risk for infection). Accordingly, the patient was referred for exchange of her CVC for a TIVAD.

Results: A TIVAD was successfully placed and the patient reported improvements in pain and ease of care compared to the CVC. She continued uneventfully with ECT resulting in better tolerability of the procedure and improvement in her mood

Conclusion: TIVADs may be appropriate alternatives for patients requiring ECT without peripheral IV access. Larger longitudinal studies are warranted to investigate the efficacy and cost-effectiveness of TIVAD and other devices as alternative VAD for anesthetic administration in patients undergoing ECT.

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Post-mortem RNAseq analysis of the overlap between depression, suicidality, and alcohol use

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Background: Alcohol use disorder (AUD) leads to a substantial increase in the risk of suicide. Understanding the alterations in a patient's transcriptome with alcohol and how the transcriptome of suicidal patients overlaps with alcohol use is a critical step toward identifying potential treatment targets. In this exploratory study, we conducted a comprehensive analysis of RNAseq data obtained from the postmortem brains' dorsolateral prefrontal cortex of intentional suicide victims without AUD, patients who overdosed on alcohol, patients who died from other medical causes but had depression, and control patients with no psychiatric co-morbidity.

Methods: Our study encompassed individuals with alcohol misuse disorder (n = 13), intentional suicide (n= 13), MDD (n=8), and controls with no psychiatric co-morbidity(n=23) as diagnosed by DSM-5 criteria from a panel of clinicians. Postmortem interval (PMI) was calculated as the duration between death and tissue preservation. Cortical dissections utilized a 4 mm punch from the dorsolateral prefrontal cortex, yielding approximately 100 mg of tissue. Cerebellar pH was measured. RNAseq using Illumina HiSeq2000 platform was utilized with FastQC being used for quality assessment of the sequences. Differential expression analysis employed R and Bioconductor packages limma and edgeR, with genes having CPM > 1 retained for analysis. The linear model formula encompassed diagnosis, age, RIN, PMI, cerebellar pH, and sex and compared all the samples relative to control samples. Pathway analysis was performed using ShinyGo with Go biological process and human species as input criteria.

Results: AUD samples yielded 70 differentially expressed genes (DEGs), MDD samples yielded 108 DEGs, and suicide samples yielded 27 DEGs relative to control samples. Pathway analysis using ShinyGo showed that AUD DEGs generally affected the regulation of glucagon, epinephrine, and vitamin pathways. MDD DEGs affected synaptic processes and signaling while suicide DEGs oddly affected pathways for reproductive processes. Out of the DEGs, AUD and MDD shared SLC16A1 as a common gene that was differentially expressed. AUD and suicide samples shared METTL21C and ZWINT as DEGs. MDD and suicide samples shared NHLH1 as a DEG. No DEG was found to be common to all three samples.

Conclusions: The results of our investigation reveal that AUD elicit modifications in both shared and distinct biological pathways with suicide and MDD samples when compared to control subjects. These novel findings provide fresh insights into the mechanisms through which AUD triggers alterations in signaling pathway levels that can alter suicidal behavior.

HOPE: A Pilot Study of Group Enhanced Psilocybin Assisted Therapy in Patients with Cancer

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Background: Psilocybin-assisted psychotherapy shows promise in treating depression and existential distress in people with serious medical illness. However, its individual-based methodology poses challenges for scaling and resource availability. The HOPE trial (A Pilot Study of Psilocybin Enhanced Group Psychotherapy in Patients with Cancer) is an IRBapproved open-label feasibility and safety pilot study examining psilocybin-assisted group therapy in cancer patients with a DSM-5 depressive disorder (including major depressive disorder as well as adjustment disorder with depressed mood). We report here the safety and clinical outcome measures including 6-month follow up data.

Methods: Outcome measures were collected at baseline, 2-week and 26-weeks post intervention. The study involved three group preparatory sessions, one high-dose (25mg) group psilocybin session, and three group integration sessions with cohorts of four participants over a three week intervention.

Results: 12 participants completed the trial. No serious adverse events attributed to psilocybin occurred. The primary clinical outcome measures of change in symptoms of depression on the clinician administered 17-item-HAM-D showed clinically substantial decrease in HAM-D scores from baseline to the 2-week timepoint (21.5 to 10.09, $p<0.001$) and the 26-week timepoint (21.5 to 14.83, $p=0.006$). Six out of twelve participants met criteria for remission at 2 weeks, as defined by HAM-D < 7, three out twelve demonstrated a clinically significant change (4-6 points), and eight out of twelve demonstrated a clinically substantial change (7-12 points).

Conclusions: This study demonstrated the safety and feasibility of group psilocybin-assisted therapy with a strong suggestion of clinical efficacy in treating depressive symptoms. Group format psilocybin-assisted therapy represents a promising model for expanding access with this highly resource intensive intervention.

A Pilot Study of SAINT in Bipolar I Depression

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Background: Repetitive transcranial magnetic stimulation (rTMS) may be an effective treatment for bipolar I depression, but current data is limited and consensus is lacking on the most effective rTMS protocol[1]. Accelerated rTMS protocols address concerns over the financial and time burdens of standard rTMS treatments which are typically delivered an hour a day for 4-6 weeks. Intermittent theta-burst stimulation (iTBS) has emerged as a more efficient form of rTMS, further reducing treatment session durations to just three minutes, while maintaining comparable antidepressant effects. The Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) is an accelerated iTBS protocol cleared by the FDA for treatment of major depressive disorder based on recent studies showing rapid efficacy after only five days of treatment[2]. This pilot study examined the safety, tolerability, and efficacy of SAINT for bipolar I depression.

Methods: This was an open-label multisite pilot study. SAINT utilizes fMRI to identify an individualized target for each participant based on where their left Dorsolateral Prefrontal Cortex (LDLPFC) is most anticorrelated with their Subgenual Anterior Cingulate Cortex (sgACC). Participants then undergo ten sessions of iTBS a day for five consecutive days. Each session consists of 1,800 pulses with 50 minute intersession intervals. Treatment is delivered at 90% resting motor threshold adjusted for cortical depth. The primary outcome was change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to the immediate follow-up visit. The Young Mania Rating Scale (YMRS) was administered twice every treatment day to monitor for development of mania. The Cambridge Neuropsychological Test Automated Battery (CANTAB) was conducted before and after treatment to monitor for cognitive changes. Discomfort during treatment was rated by each participant after every session on a ten-point scale, with 0 equal to no discomfort.

Results: Eight of ten planned participants have completed treatment, five at Johns Hopkins University and three at University of Texas at Austin. Seven completed treatment per protocol; one participant had a one-day interruption in treatment due to provider availability, but completed five days total. In the intent-to-treat analysis, average decrease in MADRS from baseline to follow-up was 16.875. Three participants met remission criteria (defined as MADRS score of 10 or less) at immediate and two more by one-month follow up. The highest YMRS score throughout treatment was 3. One participant reported headache, but no other side effects were reported. Two participants rated treatment site discomfort 5-6 by end of treatment, with the remainder reporting discomfort 3 or less. Neuropsychological testing demonstrated no negative cognitive changes and found improvement in tests assessing participants' ability to manage multitasking and the interference of incongruent task-irrelevant information on task performance (i.e. a Stroop-like effect), as well as outcome measures related to risk taking, quality of decision-making, decision time, risk adjustment, delay aversion and impulsivity.

Conclusions: We found patients responded well to treatment with SAINT without notable side effects or development of hypomania or mania. Further investigation with a larger sample is warranted to establish its treatment efficacy.

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National Network of Depression Centers

Elevated Inflammatory Markers and Cognitive Deficits in Patients with Bipolar Disorder

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Background: Deficits in various domains of cognitive functioning have been identified in patients with bipolar disorder (BD). Evidence suggests that changes in peripheral biomarkers related to inflammatory pathways are linked to neuroprogression. Our goal in the present study was to examine 1) inflammatory markers (i.e., serum levels of C-Reactive Protein [CRP], Interleukin [IL]-6 and Tumor Necrosis Factor [TNF]-α) among patients with bipolar disorder compared to healthy controls; 2) the association between inflammatory markers and cognitive functioning within the BD sample.

Methods: As part of an ongoing longitudinal study, 83 BD patients (mean age: 40.8 ± 14.7; 60% women; 81% White) and 48 healthy controls (HCs) were recruited from Boston, MA and surrounding areas. Participants were assessed by The Structured Clinical Interview for DSM-5 to confirm eligibility. Depressive and manic symptoms were respectively assessed by the Hamilton Depression Rating Scale and the Young Mania Rating Scale. Cognitive functioning was assessed by six domains of MATRICS consensus cognitive battery (MCCB) and California Verbal Learning Test (CVLT). All scores were age and sex adjusted using MCCB normative data. Multiple linear regression analyses were performed to determine the associations between inflammatory markers, and MCCB composite score controlling for medications, current depressive, and current manic symptoms. A composite inflammation index of CRP, IL-6 and TNF-α was formed to minimize type I error. This decision was supported by the results of principal component analysis (PCA).

Results: Most BD patients (79.5%) were diagnosed with bipolar I disorder and the remainder were bipolar II disorder. Approximately 48% had a history of psychosis. At baseline, relative to HCs, BD patients had higher levels of IL-6 and TNF-α ($p<.05$), but not CRP. Global cognition was negatively correlated with the inflammation composite ($\beta=-.29$, $p=.01$). To further explore the role of each inflammatory marker, individual regression analyses were performed. Global cognition was negatively correlated with peripheral levels of CRP ($\beta=-.27$, $p=.02$) and IL-6 ($\beta=-.30$, $p=.008$), but not TNF-α.

Conclusions: Inflammation may play a role in cognitive impairment associated with bipolar disorder. This information underscores the potential for targeted interventions that focus on the mechanisms involved, offering a promising avenue to enhance outcomes in the management of BD.

Sleep disturbances are highly predictive of major depressive disorder recurrence

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Background: Association of sleep disturbances with major depressive disorder (MDD) is well documented, yet the role of hypersomnolence in MDD is unknown.

Methods: In this longitudinal study, we evaluated symptoms and the impact of sleep disturbances over 3 years via 2 interview waves conducted from 2002 to 2015 in adult participants from the general US population in 8 states. Of 12,218 wave 1 (W1) participants, 10,931 were interviewed again for wave 2 (W2) 3 years later. Predictors of recurrence were determined using logistic regression.

Results: The 12-month prevalence of MDD was 9.5% in W1 and 12.1% in W2. Overall, 41.8% of interviewees with MDD in W1 still reported depressive symptoms in W2, and 6% experienced MDD recurrence (complete/partial remission at W1 with full episode at W2, or complete remission at W1 with partial remission at W2) (95% CI, 2.3%–2.9%). Characteristics in W1 predicting recurrent MDD in W2 included sleep dissatisfaction (relative risk [RR] 3.4; 95% CI, 2.6–4.6), insomnia with (RR 3.8; 95% CI, 2.7–5.3) or without (RR 2.2; 95% CI, 1.5–3.2) excessive daytime sleepiness (EDS), and hypersomnolence (an unrefreshing prolonged main sleep period >9 hours) (RR 5.5; 95% CI, 3.2–9.5). Compared with participants without MDD in W1 (n=10,091), participants with recurrent MDD at W2 (n=284) had more hypersomnolence (7.7% vs 1.9%), insomnia (20.4% vs 12.7%), insomnia with EDS (30.7% vs 11.3%), and global sleep dissatisfaction (37.8% vs 13.7%).

Conclusion: Sleep disturbances appear early in the care pathway and are highly predictive of recurrent MDD.

Ultrasonic deep brain stimulation: Initial results with a new device

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Background: Severe forms of depression have been linked to hyperactivity of the subcallosal cingulate cortex (SCC). The ability to deliver deep brain stimulation (DBS) to the SCC and associated circuits noninvasively and directly would maximize the number of patients who could receive treatment. Here we describe a new tool for noninvasive DBS and its application to two individuals with treatment-resistant depression.

Methods: We developed a non-significant-risk device, called Diadem, for effective noninvasive modulation of deep brain circuits. The device uses ultrasound arrays to directly measure and compensate for attenuation and distortion of ultrasonic waves by the head. Two individuals with severe, treatment-resistant, non-psychotic depression were enrolled into an IRB-approved experimental protocol (NCT05301036). MRI was used to coregister the ultrasound device to the subjects' brain anatomy and to measure neural responses to stimulation.

Results: Brief 30-ms pulses of low-intensity ultrasound delivered into the SCC target every 4 s caused a robust decrease in functional MRI activity within the target (corrected $p < 0.05$) in each of two sessions with each participant. One subject received repeated brief stimulation of three anterior cingulate targets during a single 2-hour session. Unexpectedly, the subject's depressive symptoms resolved within 24 hours and remained in remission for at least 6 weeks afterwards.

Conclusions: This new device illustrates the potential for noninvasive ultrasonic DBS to precisely engage deep neural circuits and to trigger a durable therapeutic reset of those circuits.

Mitigation of Ketamine-Benzodiazepine Interaction in the Treatment of Major Depressive Episodes

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Background: Coadministration of benzodiazepines (BNZs) to patients receiving intravenous (IV) ketamine for major depressive illness has been shown to reduce the effectiveness of the ketamine treatment.[1,2] In retrospective evaluations of naturalistic studies, higher doses of BNZs were associated with reduced antidepressant benefit to ketamine treatment, suggesting that reductions in concomitant BNZ use may be a prudent course of action during ketamine treatment.

Methods: We retrospectively evaluated Montgomery Asperg Depression Rating Scale (MADRS) scores in patients receiving IV ketamine in whom BNZ dosage was limited to lorazepam equivalent 2 mg/day *and* the morning dose BNZ was held on the day of treatment (n = 18) to patients not receiving concomitant BNZs (n = 49). The extent of improvement from baseline to 24 hours after the third round of IV ketamine was compared with an unpaired, two-tailed t-test.

Results: The MADRS scores of patients receiving limited BNZ dosage (baseline 27.2 $\pm$ SD 4.7; after 3rd treatment 9.8 $\pm$ 9.08; $P < 0.0001$) and patients not receiving BNZ (baseline 27.8 $\pm$ SD 6.2; after 3rd treatment 10.8 $\pm$ 9.0; $P < 0.0001$) improved significantly from baseline to 24 hours after the first treatment, and there was no difference in the extent of improvement between the two groups (BNZ 17.4 $\pm$ 9.79 vs. no BNZ 16.9 $\pm$ 8.99, $P = 0.83$; t = 2.00).

Conclusions: Limiting the dosage of BNZ to no more than 2 mg or lorazepam equivalent daily and holding the morning dose on the day of IV ketamine treatment appears to mitigate the potential interference of the therapeutic ketamine effect when the two drugs are coadministered. This is a useful strategy that minimizes disruption to ongoing treatment in patients receiving adjunctive IV ketamine.

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Pharmaceutical Pipeline of BI 1358894: Clinical Evidence for an Emerging Drug for the Treatment of Mental Health Conditions

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Objective: Amygdala hyperreactivity is thought to be a major contributor to anxiety and mood disorders, with associations to both posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). Inhibition of transient receptor potential canonical (TRPC) 4/5 ion channels, which are highly expressed in human and rodent amygdala, may reduce anxiety and stress-related symptoms by reducing amygdala hyperreactivity. Here, we provide an overview of early studies into BI 1358894; a small-molecule inhibitor of TRPC4/5 ion channels, which may provide a novel mechanism of attenuating amygdala hyperreactivity to treat symptoms in disorders such as PTSD and MDD.

Design: Five Phase I studies were performed in healthy male volunteers. Pharmacodynamic effects of BI 1358894 versus placebo were assessed following cholecystokinin tetrapeptide (CCK-4) administration to induce panic symptoms in healthy volunteers. Functional magnetic resonance imaging (fMRI) was used to investigate the effects of BI 1358894 on amygdala reactivity in patients with MDD during exposure to negative emotional faces and scenes.

Results: Across the clinical studies, BI 1358894 ≤200 mg was generally well tolerated. Compared with placebo, BI 1358894 reduced the physiological and psychological response to CCK-4, measured by the Panic Symptom Scale and levels of stress biomarkers (adrenocorticotropic hormone and serum cortisol), indicating target engagement. A fMRI study in patients with MDD demonstrated that BI 1358894 attenuated activity in the amygdala in response to negative emotional faces and scenes.

Conclusion: Ongoing Phase II trials will determine the potential for BI 1358894 in the treatment of PTSD and MDD.

Disclosures: This study was funded by Boehringer Ingelheim (1402-0001, NCT03210272; 1402-0002, NCT03754959; 1402-0003, NCT03854578; 1402-0005, NCT03904576; 1402-0008, NCT03875001). **BS**, **JC**, and **JD** are employees of Boehringer Ingelheim Pharmaceuticals Inc. **SJ**, **LL, IA** and **SDS** are employees of Boehringer Ingelheim International GmbH.

The Relationship Between Anhedonia, Reward Circuitry, Childhood Trauma and Stress

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Objective: Anhedonia, the lack of pleasure and loss of interest in activities that were once found enjoyable, is a key criterion of Major Depressive Disorder (MDD). Traumatic childhood experiences are associated with a higher risk for adult depressive disorders. The link between anhedonia, reward processing deficits and past trauma has recently gained attention. In the current study we examined the association of anhedonia and reward processing with childhood trauma and current stress. We hypothesized that 1) anhedonia would be associated with adverse childhood experiences (ACE) and perceived stress, while controlling for depressed mood and 2) BOLD signal in the reward regions (ventral striatum; nucleus accumbens) would be associated with anhedonia and childhood trauma.

Methods: The total sample consisted of 53 participants (32 with MDD and 21 healthy controls) recruited from the Harrisburg community and surrounding areas of Central Pennsylvania. As part of a larger study, participants filled out online, self-report questionnaires, measuring anhedonia (Temporal Experience of Pleasure Scale (TEPS: low TEPS score reflects high Anhedonia and Snaith Hamilton Pleasure Scale; SHAPS: higher score reflects higher anhedonia), depression (Patient Health Questionnaire: PHQ9), childhood trauma (adverse childhood experiences: ACE), and current perceived stress (Perceived Stress Scale: PSS). Participants also underwent functional magnetic resonance imaging (fMRI) while completing the reward-based Monetary Incentive Delay (MID) task. Pearson product moment bivariate and partial correlations were calculated.

Results: Anhedonia was positively correlated with childhood trauma ($r=-.49$, $p<.001$) and perceived stress ($r=-.57$, $p<.001$). Depression was also positively correlated with traumatic childhood experiences ($r=.28$, $p=.04$) and perceived stress ($r=.84$, $p<.001$). However, when controlling for depressed mood (item 2 from the PHQ-9) and anhedonia (item 1 from PHQ9), respectively, significant correlations were found only between anhedonia and childhood trauma ($r=-.38$, $p=.007$) and between depression and perceived stress ($r=.54$, $p<.001$). BOLD signal in the RNAcc was negatively correlated with traumatic childhood events ($r=-.43$, $p=.02$) only.

Conclusion: Anhedonia and reward processing deficits are specifically associated with increased traumatic childhood experiences, while depressed mood is associated with current perceived stress. This may have important implications for treatment and the neural mechanism underlying the development of anhedonia. This may also explain why depressed mood is potentially a more modifiable target during interventions by focusing on current stress, in contrast to anhedonia which is linked to past trauma. Further research investigating the temporal relationship between adverse childhood events and anhedonia is warranted to better understand and target anhedonia.

Association between chronotype and inflammation in bipolar disorder: a pilot study

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Background: Bipolar disorder (BD) is a debilitating chronic psychiatric illness associated with severe mood episodes, disruptions in activity and energy levels, changes in sleep, as well as cognitive dysfunction and poor functional outcomes. Circadian dysregulation has been proposed as a potential pathophysiological mechanism of BD given that many of the illness disturbances are regulated by circadian function; however, more research is needed to fully understand this potential mechanism. For example, despite the strong evidence of immune dysregulation in BD, few studies have examined the relationship between circadian disruption and inflammation. Additionally, the evidence is mixed regarding whether circadian dysregulation is a trait marker of BD or is mood state dependent. Therefore, we set out to examine the relationship between chronotype and circadian rhythm with markers of peripheral inflammation, illness characteristics, current mood symptoms, and functional outcomes in individuals with BD compared to healthy controls (HCs).

Methods: As part of an ongoing longitudinal study, self-reported chronotype (phase preference: morningness or eveningness) and circadian rhythm stability (e.g., flexible or rigid) and amplitude (e.g., languid/vigorous; assessing the impact of disrupted sleep on daytime energy) were assessed using the Horne–Östberg Morningness–Eveningness Questionnaire and Circadian Type inventory, respectively, in 84 patients with BD (69% female; mean age of 43 years) and 42 HCs. ANCOVAS, t-tests, Pearson Product Moment Correlation, and regression analyses were used, when appropriate, to determine the association between chronotype and circadian rhythm stability and amplitude with markers of peripheral inflammation [e.g., interleukin-6 (IL-6), c-reactive protein (CRP), and TNFα], illness characteristics derived from the SCID-5 (e.g., number of mood episodes, most recent mood episode type, duration of illness, number of suicide attempts), current mood symptoms (Hamilton Depression Rating Scale and Young Mania Rating Scale total scores), and functioning (World Health Organization Disability Assessment Schedule and the University of California, San Diego Performance-Based Skills Assessment).

Results: At baseline, there were no significant group differences in chronotype/phase preference (p = .21) or circadian rhythm stability (CTI-FR; p = .77); however, BD patients had lower circadian amplitude such that they were significantly more languid than HCs (p< .001). Within BD patients**,** chronotype/phase preference and circadian rhythm stability and amplitude did not differ by bipolar diagnosis (BD1 vs BDII) and were not associated with age, illness characteristics or mood symptoms (all ps >.05). Evening chronotype and lower circadian amplitude were associated with worse functioning (all ps < .05). Relative to HCs, BD patients had higher levels of IL-6 (p <.05) and TNFα (p < .05), but not CRP (p =.30) controlling for BMI, age, and sex. A tendency towards morningness was associated with higher levels of IL-6 (ps < .05) but not CRP or TNFα (ps > .05) controlling for BMI, age, and sex in patients, but not healthy controls.

Conclusions: Contrary to recent reports, BD was not associated with an evenness chronotype or circadian rhythm instability in our sample**;** however, we found evidence of lower circadian amplitude (e.g., more languid) in patients with BD compared to healthy controls. Patients reporting significantly higher sensitivity to sleep reductions and more lethargy following reduced sleep or an evenness chronotype exhibited functional impairment making both highly desirable treatment targets. Interestingly, higher levels of peripheral inflammation were related to morning chronotype. Further research with objective measure of circadian rhythms and immune response are needed.

An update on the efficacy of single and serial intravenous ketamine infusions for bipolar depression: a systematic review and meta-analysis.

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Background: Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid antidepressant and antisuicidal effects in treatment-resistant depression (TRD). A prior metanalysis has shown improvement in depressive symptoms after receiving a single infusion of ketamine, particularly in anhedonia and suicidal ideation. Recent serial ketamine infusions study has shown consistent improvement until 1 week after treatment. Here, we conducted an updated systematic review and meta-analysis to appraise the current evidence on the efficacy and tolerability of single and serial infusions of ketamine for bipolar depression.

Methods: A protocol was developed for this systematic review following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and registered in Open Science Framework (osf.io/9u8fp). Major databases were searched for open-label and randomized controlled trials (RCTs) that focused on single or multiple infusion of ketamine. Data for response/remission were analyzed. Statistical analysis was conducted with R software using the meta and metaprop software packages in RStudio using the DerSimonian and Laird random effects model to summarize effect sizes and pooled prevalence with logit transformation.

Results: A total of 2655 articles were screened; 9 studies were included in the systematic review. 8 studies were included in the meta-analysis (6 open-label, N=139; 2 RCTs, N=30), mean age 42.58 ±13.1 years and 54.5% were females. Pooled analysis from 2 RCTs showed significant improvement in depression symptoms measured with MADRS (1 day WMD =−11.07; 95% CI −12.3,-9.9, and 2 days WMD =−12.03; 95% CI −13.24,-10.82) after receiving a single infusion of ketamine. Open label studies (n=6) showed significant response (58%, CI=38-77%, p <0.001) and remission rates (39%, CI=26–52%, p <0.001) at study endpoint. Single infusions response rates (54%, 95% CI 44-65%, p<0.001) and remission rates were significant (28%, 95% CI=18-37%, p <0.001) at study endpoint. Serial ketamine infusions (3 open-label studies) showed a significant response rate (70%, CI= 57-83%, p< 0.001) at 3 weeks. Included studies in the systematic review also reported improvement in suicidal ideation and anhedonia after ketamine infusions.

Conclusions: Single and serial IV ketamine infusions are a promising treatment for bipolar depression at least in the short-term. However, there is a lack of long-term studies investigating IV ketamine for bipolar depression. Further studies with larger sample size are required to strengthen the evidence.

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The Effect of Clinical Repetitive Transcranial Magnetic Stimulation on Glutamatergic Neurometabolites: A Preliminary Meta-Analysis of Proton Magnetic Resonance Spectroscopy Studies in Depressed Populations

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Background: Repetitive transcranial magnetic stimulation (rTMS) alleviates symptoms of major depressive disorder and other psychiatric conditions, but the neurobiological mechanisms of its antidepressant effect remain to be fully understood. Growing evidence from proton magnetic resonance spectroscopy studies suggests that rTMS alters excitatory and inhibitory neurometabolites.

Methods:
Eligible studies that quantified Glutamate (Glu), Glutamate + Glutamine (Glx), or GABA before and after a clinical rTMS intervention in depressed patients were sourced from PubMed, MEDLINE, PsychInfo, Google Scholar, and primary literature following PRISMA guidelines. Data from 10 eligible studies were pooled using a random effects model. Cohen's d effect sizes were calculated and moderators, such as cortical region, ^{1}HMRS sequence, and rTMS intensity, were assessed. It was hypothesized that rTMS would increase glutamatergic and GABAergic neurometabolites at the rTMS stimulation site and downstream regions.

Results:
Within-subjects data from 183 cases encompassing 31 neurometabolite effects (k) were analyzed. Active rTMS in clinical responders (n=130; k=22) nominally increased glutamatergic neurometabolites (d=0.15 [95% CI:-0.01, 0.30], p=0.06). No change was found in clinical non-responders (n=54; k=7; d=-0.05 [95% CI:-0.44,0.34], p=0.8) or sham rTMS participants (n=25; d=-0.21 [95% CI:-0.70,0.28], p=0.39). A significant increase was identified in Glx (k=6 d=0.379 [95% CI: 0.09,0.67], p=0.01), but not Glu (k=8 d=-0.068 [95% CI: -0.34,0.21], p=0.6). Importantly, effect size across conditions was associated with the number of rTMS pulses patients received (p=0.05), suggesting dose dependence. Voxel size, rTMS frequency, and rTMS intensity were not associated with neurometabolite effect size.

Conclusions and Relevance: Clinical rTMS is associated with a nominal, distributed, and dose-dependent increase in glutamatergic neurometabolites, suggesting that rTMS may induce glutamate-dependent neuroplasticity and upregulate glutamatergic neurometabolism. The disparity in effect size for Glu and Glx may stem from limitations in the methods used to quantify Glu at 3T. Future studies should investigate the behavioral implications of neurometabolite changes and leverage ultra-high field MRI techniques for improved sensitivity and spatial resolution.

Elevated Plasma Levels of Proinflammatory Cytokines in Youth at Familial Risk for Bipolar Disorder

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Background: Bipolar Disorder (BD) is a persistent and severe psychiatric condition. In 2019, it affected over 2 million individuals in the United States, primarily impacting adolescents and young adults. High-risk prospective studies have revealed increased rates of psychiatric and bipolar spectrum disorders in the offspring of adults with BD. Longitudinal data encompassing phenomenological, neurostructural, cognitive, neurochemical, and biochemical aspects have demonstrated a neurobiological progression in BD. This progression results in significant and persistent impairments in social and occupational functioning for most patients. Multiple studies have suggested that inflammatory disturbances may be involved in the pathogenesis of BD. Individuals with BD have been reported to exhibit alterations in both central and peripheral immune proteins. Notably, children with a parent affected by BD, especially those who later develop a mood disorder, show an abnormal neuroimmune state. Although mounting evidence suggests the involvement of inflammatory systems in BD, the precise role remains unclear. Observational studies indicate that early intervention can enhance disease management and outcomes, whereas delays in treatment are associated with poorer results. Currently, there are no molecular markers enabling intervention in high-risk individuals or facilitating early detection and specific treatment targets for early-onset patients. Thus, it is imperative to identify warning signs earlier and enhance intervention efforts. Based on this, we investigated inflammatory markers in plasma from children and adolescents with BD or a familial risk for the disorder.

Methods: In this preliminary study, we investigated plasma samples from 100 children and adolescents aged 7 to 17 from UTHealth's Center of Excellence in Mood Disorders. Early-onset BD (BD Youth) consisted of individuals diagnosed with BD type I, BD type II, or BD not otherwise specified. Individuals with familial risk for BD (BD Offspring) were those without affective or non-affective diagnoses at the time of enrollment and had at least one parent who meets DSM-IV criteria for BD type I or BD type II. A third group of subjects was the non-psychiatric controls (Control), who had no history of psychiatric illness, abuse of illicit substances, presence of chronic medical conditions, or family history of psychiatric disorders in a first-degree relative. The total of samples per group was 29 for BD Youth, 25 for BD Offspring, and 46 for control. Quantitative analysis of TNFα, IFN, IL1b, IL2, IL6, IL10, and IL18 plasma levels was performed using a magnetic bead-based multiplex immunoassay commercial kit. One-way ANOVA was conducted to determine whether each cytokine level differed among groups. Statistical analyses were performed by One-Way ANOVA followed by Tukey's multiple comparisons test. Outliers were removed, and age, sex, and ethnicity were used as biological variables. Data were analyzed using IBM SPSS Statistics 28 and GraphPad Prism 9. Significance levels were determined at a value of 0.05.

Results: TNFα and IL18 plasma levels were statistically significantly different between groups ($F_{(2, 87)} = 4.617$, $p = 0.0124$, and $F_{(2, 89)} = 7.069$, $p = 0.0014$, respectively). Tukey post hoc analysis revealed that both cytokines' levels increased in BD Offspring when compared to BD Youth and Control. Other cytokines levels were below the detection range.

Conclusions: Our results support the findings of the literature that individuals with familial risk have an aberrant immune state, which confirms that inflammation plays a significant role in the physiopathology of BD. Although expected to have a similar proinflammatory profile, patients with early onset BD use medication that can influence cytokine levels, a confounder that was not investigated in this study. Future perspectives include further examining the role of inflammation in BD risk and how it influences the symptoms of depression and manic episodes, as well as the functioning and cognitive scores of patients. This can help identify warning signs earlier and improve intervention efforts.

National Network of Depression Centers

Non-invasive spinal cord stimulation for MDD: A pilot randomized controlled trial

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Background: Longstanding theoretical frameworks suggest a role and therapeutic potential for spinal pathways in major depressive disorder (MDD). We aimed to evaluate the antidepressant effects and tolerability of transcutaneous spinal direct current stimulation (tsDCS) in MDD.

Methods: This was a double-blind, randomized, sham-controlled, parallel group, pilot clinical trial in unmedicated adults with moderate MDD (NCT03433339). The study was funded through a Brain and Behavior Research Foundation Young Investigator Award (#26649). Twenty participants were randomly allocated (1:1 ratio) to receive "active" 2.5 mA or "sham" anodal tsDCS sessions (20 min each) with a thoracic (anode; T10)/right shoulder (cathode) electrode montage 3/week for 8 weeks. Change in depression severity (MADRS) scores (prespecified primary outcome) and secondary clinical outcomes were assessed. ANOVA models were used for statistical analysis. Additionally, an E-Field model was generated using the active tsDCS parameters.

Results: Compared to sham (n=9), the active tsDCS group (n=10) showed a greater decrease in MADRS score from baseline to week 8 with a large effect size (-14.6± 2.5 vs -21.7±2.3, p=0.040, d=0.86). Compared to sham, active tsDCS induced a greater decrease in MADRS "reported sadness" (-1.8 vs -3.2, p=0.012) and a statistical trend in the same direction for "pessimistic thoughts" items, and CGI-I scores. Compared to sham, the active tsDCS group showed a greater cumulative decrease in pre/post tsDCS diastolic blood pressure. No group differences were observed in adverse events (AEs), which included mild transient erythema and non-painful itch/burning sensation, and no serious AEs occurred. The E-field simulation showed current within the neuromodulation range (maximum ~45 V/m) reached the thoracic spinal gray matter.

Conclusions: Results suggest that tsDCS is feasible, well-tolerated, and has therapeutic potential for MDD. The underlying mechanisms warrant further investigation.

Randomized Controlled Trial of Stress Management and Resiliency Training for Depression (SMART-D) vs Treatment as Usual in the treatment of Major Depression

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Background: Stress is associated with risk of development, maintenance and recurrence of major depression(MDD). Resilience is the capacity of an individual to resist negative psychological, biological and social consequences of stress. A recent open label feasibility study of Stress Management and Resiliency Training (SMART) showed positive response in depression (P<0.001), resiliency(P=0.03) and perceived stress (p=0.002). The current study aimed to compare the efficacy of augmenting SMART to treatment as usual (TAU) in a randomized controlled trial (RCT) compared to TAU alone. The intervention was modified to address specific depression related cognitive biases to create SMART for Depression (SMART-D).

Methods: In this RC, patients with MDD were randomly allocated to an adjunctive 8-week group therapy of SMART-D (6 sessions) compared to TAU alone. Random allocation, blinding of raters and statistician were followed. SMART-D encompassed attention training and practice of gratitude, compassion, higher meaning, acceptance, and forgiveness, with additional emphasis towards self, compared to TAU. Participants were followed for 6 months post intervention. The primary outcome measure was baseline-to-endpoint change in depression [Hamilton Rating Scale for Depression (HAM-D-17)]. Secondary outcome measures included baseline-to-endpoint change in perceived stress (Cohen's Perceived Stress Scale), and resilience (Connor-Davidson Resilience Scale (CD-RISC).

Results: 27 participants enrolled in the study between December 2021- June 2023 (Group 1=14, Group 2=13). (mean age 47.9±14 years, female 67%). Baseline ratings of mood were in mild-moderate symptom severity (mean HAM-D = 12.6 and PHQ-9 = 12.5). Preliminary analysis of the primary outcome, depression (HAMD) using linear mixed effects regression showed a significant Group*Time interaction, with significant difference (B=6.1 (CI=1.5-10.8, P=0.01) between the 2 groups at 3 months post follow-up. One group showed sustained improvement over 6 months. Secondary analysis of perceived stress and resilience did not show significant Group*time interaction between the 2 groups, despite showing greater improvement in 1 group. Further results are pending.

Conclusions: A preliminary analysis of a RCT of a resiliency intervention (SMART-D) in patients with MDD, shows evidence of significant treatment response, that was maintained over 6 months post intervention in 1 group compared to the other group. Further analysis and conclusions will be reported shortly. Limitations are a small sample size despite a robust clinical trial design that might limit the power to detect statistical differences between groups.

Change in Neurocognitive Functioning in Patients with Treatment-Resistant Depression with Serial Intravenous Ketamine Infusions: The Bio-K Multicenter Trial

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Background: Major depression is associated with significant impairment across different neurocognitive domains. Intravenous (IV) ketamine has been repurposed as a robust and rapid-acting antidepressant for treatment-resistant depression (TRD). There are limited data on the impact of IV ketamine and change in cognition.

Methods: This was a multicenter open-label clinical trial where we enrolled adult (18-65 years of age) patients with TRD, who received *three* IV ketamine infusions (0.5 mg/kg) within 11 days (acute-phase). A subset of patients who remitted at the end of acute phase received additional *four weekly* infusions at the Mayo Clinic site. We used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) to assess cognitive functioning before the IV ketamine infusion (baseline), at the end of acute series (24 hours post infusion #3) and at the end of continuation phase (24 hours post infusion #3).

Results: 74 patients (mean age 44.4± SD 12.9 years, 62% females, mean MADRS score 28.0±SD5.8) received at least 3 IV ketamine infusions, of which 70 patients completed the baseline and endpoint RBANS. There was a significant improvement in the depression symptoms at the end of acute series, with 53% remission rate. Except language domain, there was no significant difference in the baseline neurocognitive domain scores between the remitters and non-remitters. Better baseline language performance (semantic fluency) correlated with greater improvements in MADRS at the end of acute phase. RBANS index analyses using mixed-effects models suggest significant improvement in memory (immediate and delayed), language, and attention at the end of acute phase, memory improvement continued to persist even after adjusting for changes in depression scores. There was no significant change in the visuoperception domain scores. Baseline depression did not correlate with improvement in cognition. Improvement in depression was associated with improvement in immediate memory. In a sub-group of 20 patients at the Mayo site where remitters received four additional weekly infusions, there were sustained improvements in memory (immediate and delayed), and attention. There was further improvement in visuospatial and language domain scores by the end of the continuation phase among this sub-cohort.

Limitation: Open-label study design. Patients continued their psychotropic medications.

Conclusions: This study supports the evidence that there is absence of deleterious effect on cognition among patients with TRD with serial IV ketamine infusions in short-term and in fact ketamine may have a procognitive effect in patients with TRD. These findings need to be replicated in a large sample size study with greater power to explore if improvement in depression is moderating the change in cognition. If replicated, long-term effects of IV ketamine need to be evaluated.

Trial Registration: ClinicalTrials.gov: NCT03156504

PTSD symptoms as a predictor of higher depression severity in anxiety clinic patients

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Background:

Anxiety has long been associated with mood disorder comorbidities despite remaining a diagnostically distinct entity. It has been suggested that this association may be related to possible overlap of diagnosis criteria or partially due to shared genetic predispositions. However, there is still lack of emphasis on PTSD screening significance or the impact of PTSD symptoms on anxiety severity. There are currently no recommendations of PTSD screenings in anxious or depressed patients or cut-off scores in self-reported instruments that indicate simultaneous presence of PTSD. Patient administered questionnaires such as PHQ-9 and GAD-7 have been validated instruments to assess the severity of depression and anxiety symptoms, respectively. Here, we assess the correlation between GAD-7 and PHQ-9 and the relationship with PTSD, amongst patients from our anxiety clinic.

Method:

Patients treated at our institution's anxiety clinic were given the PHQ-9 and GAD-7 to fill out prior or during their initial intake assessment. The patients' primary diagnoses and comorbidities were documented. A bootstrapping technique, with 1,000 iterations, was employed to estimate the partial correlation between the PHQ-9 and GAD-7 scores. Separate Bayesian regression analyses were conducted to predict GAD-7 and PHQ-9 scores. PTSD diagnosis was used as independent predictors, while controlling for age.

Results:

The sample included 83 subjects. The mean (± SD) age was 39.25 ± 14.21. 10.84% were males. The average GAD-7 and PHQ-9 scores were 11.22 ± 5.88 and 9.96 ± 6.85, respectively. The prevalence of MDD, Panic disorder, and PTSD symptoms as comorbidities were 60.24%, 34.94% and 34.94%, respectively. After adjusting for age, the bootstrapped correlation coefficient between GAD-7 and PHQ-9 scores was 0.74. The 95% confidence interval for this correlation coefficient ranged from 0.63 to 0.83.

For GAD-7 scores, the posterior mean ± SD, 3% highest density interval (HDI), and 97% HDI for the age coefficient were -0.017 ± 0.046 and [-0.107 - 0.067]. For the PTSD coefficient, values were 3.051 ± 1.337 and [0.553 - 5.584]. For PHQ-9, values were -0.046 ± 0.054 and [-0.145 - 0.054] for the age coefficient; for the PTSD coefficient, values were 2.521 ± 1.565 and [-0.257 – 5.622].

Regarding the association between PTSD and the scores, 98.75% of the posterior distribution for the PTSD coefficient in predicting GAD-7 scores was above zero, and 94.91% for predicting PHQ-9 scores.

Discussion:

In our sample, we found a positive relationship between the GAD-7 and PHQ-9 scores, after adjusting for age. A PTSD diagnosis had a very high chance of predicting higher scores in both GAD-7 and PHQ-9, after adjusting for age. This highlights the importance of screening for comorbid diagnoses, especially PTSD, in patients with anxiety.

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Fast-Forwarding the Clock: The Accelerated Aging Phenomenon in Bipolar Disorder

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Background: Bipolar Disorder (BD) is associated with an approximately 10-year decreased life expectancy[1]. While unnatural causes, including suicide, contribute to a 30-60-fold increased risk of mortality in patients with BD compared to the general population, suicide alone is responsible for less than a quarter of all lost life years[1]. Instead, death by natural causes is the leading contributor to premature death in patients with BD[1]. Therefore, it has been hypothesized that pathways that result in BD may also contribute to accelerated aging[1]. In addition to an increased rate of decline in clinical markers of cognition and physiologic functioning, the theory of accelerated aging in BD is supported by the findings in several biomarkers from across organ systems[2,3]. A promising biomarker is "Brain Age": a prediction of age using structural neuroimaging measures[2-5]. Brain Age has been used to predict increased mortality[4] and having an older predicted age than chronological age has been repeatedly associated with impaired cognitive functioning in adults[6]. Studies of "Brain Age" in BD have been limited in scope and produced mixed results with trends suggesting a unique pattern of accelerated aging[6].

Methods: T1-weighted MRI scans were collected from 664 subjects including 304 controls, 248 patients with BD Type 1 (BD1), and 112 patients with BD Type 2 (BD2) between ages 18 and 65. All data were collected on 3T scanners from 3 independent sites. Brain Age was calculated using a model developed by the ENIGMA consortium trained to predict age from 77 neuroanatomical features including cortical thickness, surface area, and subcortical volumes[5]. Predicted Age Difference (PAD) was calculated by subtracting chronological age from Predicted Age. A regression model was used to determine the relationship between PAD and disease status. Chronological age and sex were included as covariates. Follow up Man Whitney U tests and Cohen's D were conducted to compare each group independently. Further regression models were conducted to investigate the association between clinical and other biological variables including epigenetic age and PAD in both the full cohort and the BD only cohort.

Results: Brain-PAD was significantly larger in patients with BD1 than HCs (+3.63 years vs 1.56 years, Cohen's D=0.37, p=5e-05). Conversely, no significant associations were seen between patients with BD2 and BD1 or HCs. Investigation of clinical factors associated with elevated Brain-PAD in patients with BD revealed significant associations with number of hypomanic episode (Adj R2=0.1, p<0.01) and medication status (Adj R= 0.06, p<0.05). While measures of lithium exposure were not associated, incorporation of current lithium dose yielded the strongest PAD model (β=0.0104, p<0.1, Adj R2=0.743). Tested models without lithium incorporation ranged from R2=0.2-0.5). There also was not a significant association found between PAD and epigenetic age, however, this was tested in a small subset of only 67 patients.

Conclusions: BD1 is associated with accelerated brain aging that may be mediated by age of diagnosis and medication exposure. Future analyses are needed to determine how disease burden and clinical factors affect biological aging including mediation and moderation models and ideally prospective studies. Furthermore, investigation is needed to determine the clinical utility of these biomarkers to determine if they can be used to support clinical decision making through prediction of outcomes such as treatment response.

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Trial-in-progress: Disease characteristics and real-world, standard-of-care effectiveness in patients with major depressive disorder with anhedonia and inadequate response to antidepressants

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Background: Patients with major depressive disorder (MDD), a complex, heterogeneous disorder, may exhibit varying symptom combinations[1]. Unresolved symptoms such as anhedonia (inability/reduced ability to feel pleasure) are frequent in patients treated with current antidepressants (ADs)[2]. Higher levels of anhedonia are associated with negative disease outcomes in MDD, including delayed remission, reduced chance of full recovery, vulnerability to future mood episodes, disease chronicity and treatment resistance, impaired functioning, and increased suicidality risk[3]. In patients with MDD and inadequate response to first-line ADs, anhedonia prevalence, clinical presentation, severity, persistence, and time-course are ill-described. Furthermore, clinical practices and treatment strategies in these patients are based on "trial and error"; current treatment approaches are not selected based on symptom profile and underlying neurobiology[4,5]. The main aims of this real-world study are to describe the socio-demographic, disease-related, and treatment-related characteristics, and standard-of-care treatment patterns, of patients with MDD with anhedonia with inadequate response to their current AD, and to assess the link between response prediction and underlying neurobiology.

Methods: This is an observational, prospective, non-interventional, multinational, 12-month study of adult patients (18-64 and 65-74 years) with MDD who have had an inadequate response to their current AD and for whom a new AD is being considered to manage symptoms. Approximately 500 patients with MDD will be enrolled from >100 routine clinical practice sites. Data collection, including treatment response to current ADs, will occur at baseline when a new AD treatment is initiated (i.e., any new pharmacological or non-pharmacological treatment prescribed in addition to the current AD treatment). Subsequently, patients will be followed through a 12-month observation period during which data will be collected at 6 weeks, 6 months, and 12 months. Additional data will be collected during event-driven time points, or upon early study withdrawal/discontinuation, when indicated. Primary data sources will be medical records and standardized clinical outcome assessments. Blood sample collection for biomarker analysis and digital biomarker collection will be optional. Effectiveness will be evaluated overall, and by anhedonia and insomnia severity at study entry. Safety will be monitored throughout the study.

Results: Enrollment initiated in April 2023 and recruitment actively ongoing.

Conclusions: By characterizing MDD with anhedonia, we will support evolving the current treatment strategies from "trial and error" towards a more targeted, precision medicine approach.

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Characterizing the Subjective Experience of Psychedelic use in Individuals with Bipolar Disorder

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Background: Recent research shows that patients with bipolar disorder (BD) find more benefit than harm from using psychedelics such as psilocybin (Morton et al., 2023). Here we ask the question - How do patients with BD feel about classic psychedelics and the experiences they produce? Do patients with BD report having a positive "mystical" experience; Or, do they report a more negative or "challenging" experience after using a classic psychedelic? In our ongoing study we asked patients experiencing BD who have either tried ("users") or have been contemplating trying ("non-users") a psychedelic about their experiences. Specifically, we use the Mystical Experience Questionnaire (MEQ) and Challenging Experience Questionnaire (CEQ) to ask - Does the experience of psychedelics differ between users and non-users, and what are the implications of this difference?

Methods: We collected data from 145 participants (n=145); 97 users and 45 non-users thus far. All participants were age 18 or older, diagnosed with BD, and gave written consent to participate. This data is part of an overarching study which includes a calendar-based interview. Before the interview portion of the study, we administered two questionnaires to assess participant's subjective experiences: **1)** Mystical Experience Questionnaire: The MEQ is a 30-item self-report questionnaire that assesses discrete mystical experiences brought on by classic hallucinogen use (Barret et al., 2015). It is used to assess key aspects of the psychedelic experience - positive mood, transcendence (i.e., an experience beyond the normal or physical level), ineffability (i.e., incapable of being expressed or described in words), and mysticism (i.e., the subjective feeling of unity and interconnectedness and is often reported in religious contexts), and is focused on the acute subjective effects of the psychedelic (Barrett et al., 2015). **2)** Challenging Experience Questionnaire: The CEQ is a 26-item self-report questionnaire used to assess whether the person experienced any adverse or negative psychological reactions to psychedelic use. There are 7 sub-scales - fear, grief, physical distress, insanity, isolation, death, and paranoia, which are focused on the acute effects of the psychedelic experience (Barret et al. (2016).

Results: 1) MEQ: We ran a MANOVA to test for differences between users and non-users, and we found a trend, $F_{(4,137)} = 2.24$, $p = 0.07$) which led us to investigate further. Looking at the univariate analyses, it emerged that the trend is being driven solely by the subscale "ineffability" scale, such that users showed a trend for greater scores on ineffability comparted to non-users, $F_{(1,140)} = 1.032$, $p = 0.76$, *partial eta squared* = 0.007. **2)** CEQ: the MANOVA comparing users and non-users, revealed a significant overall effect, $F_{(7,134)} = 2.79$, $p = .01$. Univariate analyses showed significant effects for the subscales fear, physical distress, insanity, death, and no effect for grief, (all *p-values* < .05, but not the subscales, isolation and paranoia). Lastly, we found 22% of users reported having a "complete mystical experience" according to the MEQ scoring, and we will explore whether this is related to mental health using the calendar-based Time Line Follow-Back.

Conclusions: Our research suggests that users' experiences differ to some degree from what people with BD expect to experience when they just have considered trying psychedelics but have not (yet) done so. When it comes to ineffability, patients with BD who have tried a psychedelic report a higher percentage of ineffability than non-users. Further, our data suggests that people who have contemplated using but not yet used anticipate more challenging and negative experiences compared to actual reports from users. Specifically, non-users expect to experience more fear, physical distress, insanity, and even death-like experiences when asked about the anticipated experience to psychedelics. Overall, our findings highlight the importance of educating and preparing participants ('set') for the administration of a psychedelic experience, especially if individuals have no prior experience with psychedelics.

Evaluation and Feasibility of Oura Ring in Developing Digital Phenotypes of Sleep in in Patients with Mood Disorders

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Background: There is increasing recognition of the potential to augment self-reported data with new types of digital phenotype data from commonly used smartphones and wearable devices among patients with mood disorders. Out of clinic measurement of patient's lived experiences is critical to improved understanding of the course of illness and potentially new opportunities for more timely interventions. Sleep difficulties are an important symptom in mood disorders that may especially benefit from real time digital monitoring for improved care management. We aim to assess the feasibility and acceptability of passive collection from an Oura smart ring (https://ouraring.com/) in individuals with mood disorders, and report preliminary findings of associations between sleep parameters from the Oura ring and mood related symptoms.

Methods: We conducted a pilot study of participants with major depressive disorder (MDD), bipolar disorder (BP), and healthy controls at Johns Hopkins University (JHU) and the Mayo Clinic. Treatment seeking depressed patients who are English-speaking, ages 18 and older, and not currently suicidal were included. Participants at JHU were provided an Oura smart ring to collect passive sensor data on activity, heart rate, and sleep quality. In addition, they downloaded the MindLAMP app onto their smartphones, which pushes out surveys on mood and sleep during the week and gathers the passive sensor data into a single platform for analysis. Participants also completed self-report measures about sleep, satisfaction/enjoyment of life, mental alertness, anxiety, and stress at baseline and three follow-up visits a month apart for three months. The average and standard deviation of total daily sleep time as measured by the Oura ring were calculated for each individual over the first 14 days of use. Discontinuation rates in using the Oura ring were compared between cases and controls using chi-square statistics, and differences in the means of total daily sleep time and symptom measures were compared using t-tests or F-tests for standard deviation.

Results: We report here preliminary results on 81 participants at JHU; 39 MDD and 21 BP cases (mean age=34.2, 22% male) and 21 controls (mean age=30, 47.6% male). Study discontinuation rates were 31.7% for cases and 9.5% for controls (P=0.21). Case participants provided usable Oura ring data on 55% of the follow-up days compared with 68% for controls. Average total daily sleep time measured by the Oura ring over the first 14 days of the study was greater among cases than controls ($\bar{x}$=7.25±1.08 vs $\bar{x}$=6.59±0.78, P=0.008), as was the variation in total daily sleep time over the same time period although this was not significant ($\bar{x}$=1.45±0.55 vs $\bar{x}$=1.05±0.39, P= 0.14). Cases had higher baseline scores than controls on the PHQ-9 ($\bar{x}$=11.76±5.75 vs $\bar{x}$=1.85±2.22, P< .00001), GAD-7 ($\bar{x}$=10.03±5.19 vs $\bar{x}$=1.24±1.76, P< .00001), and PMQ-9 ($\bar{x}$=7.34±5.28 vs $\bar{x}$=1.81±3.25, P= .000014). However, neither baseline tests scores nor changes from baseline to last follow-up tests scores on any of these measures were significantly correlated with average total daily sleep time or variability in total sleep time.

Conclusions: We were able to get usable data from the Oura ring on a majority of participants, but there were differences by illness status. Preliminary analyses did not suggest any relationship between total daily sleep time and mood symptoms, but more work is needed to investigate if other sleep parameters from the Oura ring are more informative about the course of illness.

Proteomic Profiles and Their Association with Major Depressive Disorder: A Comparative Study Between NESDA and the Pritzker 500

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Background: Major Depressive Disorder (MDD) is a debilitating mental condition affecting millions worldwide. While its etiology remains multifaceted, proteomic alterations provide significant insights into the molecular underpinnings of the disease. With the advent of advanced platforms like the SomaLogic, a deeper exploration into the proteomic landscape has been made possible. The current study seeks to harness this capability to delineate proteomic variations in MDD across two distinct cohorts, offering a broader perspective on potential biomarkers and therapeutic targets. This study investigates the association between cytosine and chemokines proteomic profiles, encompassing all identified via the aptamer-based SomaLogic platform, and Major Depressive Disorder (MDD) in two distinct datasets: the Netherlands Study of Depression and Anxiety (NESDA) and the Pritzker 500 Study. The aim is to uncover patterns of protein association and their relevance to MDD.

Methods

Participants and Criteria NESDA: The study involved 1,755 participants aged between 18 and 65 years. These participants were primarily of Dutch origin and represented a broad spectrum of depression, including those without any psychiatric diagnoses, referred to as controls.

Pritzker 500: This cohort consisted of 153 participants aged between 18 and 70 years. Among these, 72 were diagnosed with Major Depressive Disorder (MDD), and the remaining 81 were controls without any psychiatric disorders. These participants were from various institutions: Stanford University, University of California, Irvine, and Cornell University.

Measurement Scales: The severity of depressive symptoms in the participants was gauged using specific scales. For participants in the Pritzker 500 Study, the Hamilton Depression Rating Scale (HDRS-21) was employed. Conversely, for the NESDA Study, the Inventory of Depressive Symptomatology Self-Report (IDS-SR) was used.

Baseline Evaluation: aBlood samples were collected from fasting participants in the morning and processed for routine clinical labs and research use. Medical comorbidities were self-reported by participants. In the Pritzker 500, Inflammatory disease was defined as the presence of one or more of the following conditions: diabetes, hypertension, hyperlipidemia, coronary artery disease, myocardial infarction, kidney disease, hepatitis, thyroid disease, asthma, autoimmune disease, cancer, and polycystic ovarian syndrome.

Proteomic Platform: Proteomics for both Pritkzer 500 and NESDA were measured using the aptamer-based SomaLogic platform. This platform was specifically designed to capture a vast range of proteins. Analyses in the study were restricted to 32 chemokines and cytokines that have been associated with psychiatric disorders, chronic disease or both.

Statistical Analysis

Cross-sectional Analysis The Pritzker 500 and NESDA datasets underwent identical analytic procedures. The SomaLogic data were subjected to Principal Component Analysis (PCA), which yielded seven principal components for each dataset. PCA included the 32 proteomic analytes as well as age and body mass index (BMI). Principal components (PCs) that had an eigenvalue >1 were retained for additional analysis. Adjusted logistic regressions were performed to evaluate the association between each PC and MDD status (compared to controls). Regression models were adjusted for sex, race and ethnicity, and psychotropic medication use. Age and BMI were not included as covariates as they were included in the PCA.

Longitudinal Analysis Repeated Measures for HDRS-21 (Pritzker 500): Depression scores were reevaluated over a one-year follow-up. Using SAS's PROC GLM in a repeated measures framework, we analyzed HDRS-21 scores, adjusting for significant confounders, including interactions with medication use.

Mixed Models for IDS-SR (NESDA): Depression scores were assessed over a two-year follow-up. Utilizing SAS PROC MIXED, IDS-SR scores were modeled over time, incorporating PCs as fixed effects and participants as random effects. The model controlled for relevant covariates and evaluated temporal interactions with medication use.

Pritzker 500 Study Cross-sectional Results: Seven PCs were extracted from the Pritkzer 500 dataset using the criterion on eigenvalue > 1. Pritzker principal component 3 (PC3) was mainly characterized by immune and inflammatory markers. The data revealed that individuals with higher PC3 scores had 1.65 times higher odds of current moderate to severe MDD compared to controls (95% Confidence Interval: 1.05 to 2.59). A further breakdown of PC3 showed higher mean scores to be positively associated with: Inflammatory disease (p < .0001), hyperlipidemia (p < .0001), hypertension (p < .0001), type 2 diabetes (p = 0.0003), and thyroid Disease (p = 0.002) Principal component 4 (PC4) exhibited a strong correlation with BMI r = 0.53. For every one unit increase in PC4, participants had 1.54 times higher odds of current moderate to severe MDD compared to controls (95% Confidence Interval: 1.01 to 2.34). A further breakdown of PC4 showed higher mean scores to be positively associated with inflammatory disease (p < .02).

NESDA Study Cross-sectional Results: Seven principal components for extracted from the proteomic data using the criterion of > 1 eigenvalue. NESDA PC3, which showed protein patterns akin to the Pritzker 500 PC3. For every one unit increase PC3 participants were found to have 1.37 times higher odds current MDD compared to controls (95% Confidence Interval: 1.16 to 1.62). Similar to Pritzker 500 findings, NESDA PC4 was closely linked with BMI. A one unit increase in NESDA PC4 was associated 1.14 times higher odds of current MDD compared to controls (95% Confidence Interval: 1.00 to 1.31).

- The Pearson correlation for PC3 across the Pritzker 500 and NESDA datasets was 0.60, indicating a moderate consistency in protein patterns across studies. For PC4, the correlation was 0.63.

Pritzker 500 Study Longitudinal Results There was an interaction PC4 and SSRI/SNRI medication use, and one-year HDRS-21 score. A one unit increase in PC4 predicted a 3-point increase in one-year HDRS-21 scores among those using SSRIs and SNRIs. There was no association between PC3 and HDRS-21 scores at one year with or without accounting for an interaction with SSRI/SNRI medication use.

NESDA Study Longitudinal Results A one unit rise in PC4 was linked to a 1.9 unit elevation in IDS-SR scores at a 2-year follow-up. PC3 was not associated with future IDS-SR score at two years follow-up. There was no interaction between either PC or SSRI/SNRI use as predicators of MDD severity.

Conclusion: Chemokine and cytokine profiles derived from proteomics showed similar patterns of association with MDD across two independent observational studies. They are consistent across different cohorts and off er predictive insights into future MDD severity. This highlights the potential of proteomic markers in understanding, diagnosing, and treating MDD.

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Mood Impacts of Hypersexuality and the Potential of Naltrexone: A Comprehensive Review of Clinical Trials and Two Case Studies

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Background: Hypersexuality, compulsive sexual behavior, and obsessive hypersexual thoughts and compulsions represent facets of a complex spectrum of sexual disorders. These conditions have profound implications beyond mere behavioral manifestations, casting a pervasive shadow on personal relationships, professional engagements, and overall mental well-being.[1] The emotional consequences, characterized by feelings of guilt, shame, and distress, can escalate into mood and anxiety disorders and even lead to suicidal tendencies.[1] The acute intensity of these symptoms poses a therapeutic challenge, particularly given the delayed efficacy of treatments like SSRIs. In this context, this review explores the potential of naltrexone, an opioid receptor antagonist, as a promising therapeutic solution.

Methods: A systematic review, adhering to PRIMA-P guidelines, was undertaken to evaluate naltrexone's role in addressing hypersexuality. Comprehensive database searches in PubMed and EMBASE yielded four relevant clinical trials. This was enriched by insights from two case studies at a Midwest inpatient psychiatric facility, focusing on individuals hospitalized due to suicidal ideation stemming from intense hypersexual obsessions.

Results: The therapeutic promise of naltrexone resonated consistently across studies.[2-5] Two RCTs highlighted its significant impact on symptom severity, as measured by the Hypersexual Behavior Inventory.[2-3] While naltrexone dosages varied from 25-100mg, a 50mg dose was predominant. One study noted naltrexone's transient negative effect on sexual arousal.[4] Interestingly, elevated prolactin levels, potentially driving sexual satiation, shed light on naltrexone's therapeutic mechanism. Both paroxetine and naltrexone showcased safety and superior efficacy compared to placebos.[2] An intriguing RCT highlighted naltrexone's role in curbing impulsive sexual behaviors in Parkinson's disease patients.[5] In the case studies, the combination of an SSRI and naltrexone led to a marked reduction in hypersexual obsessions within a day of initiation.

Conclusions: Synthesizing insights from clinical trials and real-world case studies, naltrexone stands out as a potent therapeutic ally in the battle against a complex spectrum of sexual disorders and its associated emotional challenges.

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